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ORIGINAL ARTICLE

^{1}H and ^{13}C NMR spectra of condensed benzimidazole and imidazobenzodiazepines

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^{1}H–^{13}C correlation

Abstract Benzimidazoles are heterocyclic compounds that have awakened great interest during the last few years because of their proven biological activity as antiviral, antimicrobial, and antitumoral agents. For this reason, the development of a systematic NMR study of condensed benzimidazole compounds constitutes a significant tool in understanding the molecular dynamics and the structural parameters that govern their behavior. The ^{1}H and ^{13}C NMR spectra of new imidazobenzodiazepines were investigated. Based on the study of NMR chemical shifts, we discuss the environmental effect of the nucleus ^{13}C. The correlation ^{1}H–^{13}C proved to be a useful method for distinguishing the assignment of carbon.

1. Introduction

The benzimidazole nucleus and its derivatives are known to play extremely crucial roles in the structures and functions of a number of biologically important molecules, generally by virtue of their being coordinated to metal ions. The incorporation of the benzimidazole nuclei is an important synthetic strategy in drug discovery (Townsend, 1976). The high therapeutic properties of the related drugs have encouraged the medicinal chemists to synthesize the large number of novel chemotherapeutic agents (Kleeman et al., 1999). Pharmaceutical properties including: antiviral (Cheng et al., 2005), antitumoral (Yang et al., 2009; Charlson et al., 1973), antifungal and antimycotic (Walker et al., 1978), antihistaminic and antiallergic (Nakano et al., 2000), antimicrobial (Marquis et al., 2006), antihelminthic (Mavrova, 2006) and spasmolytic activity (Navarrete-Vázquez et al., 2006). These different applications have attracted many experimentalists and theorists to investigate the spectroscopic and structural properties of benzimidazole (Mohan, 1991; Klots et al., 1997; Morsy et al., 2002) and some of its derivatives (Yurdakul and Yilmaz, 1999).

In this work, we report the study of NMR spectra of condensed benzimidazoles. We have previously described

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the synthesis of 4-(2,5,6-trimethyl-^{1}H-benzo[d]imidazol-7-ylamino) pent-3-en-2-one **1a**, ethyl 3-(2,5,6-trimethyl-^{1}H-benzo[d] imidazol-7-ylamino)but-2-enoate **1b**, 4-acetonylidene-5-acetyl-2,6, 8,9-tetramethyl-7H-imidazo-[1,5,4-e,f][1,5]-benzodiazepine **2a** and 4-acetonylidene-5-ethoxycarbonyl-2,6,8,9-tetramethyl-7H-imidazo-[1,5,4-e,f][1,5]-benzodiazepine 2b (El kihel et al., 2008). The NMR parameters of these heterocycles are reported in this paper.

2. Results and discussion

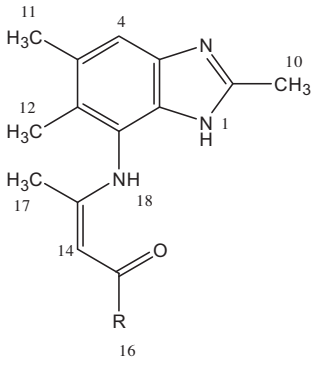
A variety of works are reported about the NMR of benzimidazole derivatives (Embrey and Craik, 1995; Infante-Castillo et al., 2008; El kihel et al., 2005) The ^{13}C NMR spectra and the charge density of carbon for the benzimidazole were reported by Pugmire and Grant (1971). The chemical shifts of carbon 13 for some benzimidazoles substituted in position 5 were published (Mathias and Overberger, 1978; Fruchier et al., 1980; Blackburn et al., 1982; Lopyrev et al., 1981, 1985). Other works have reported the NMR of some bisbenzimidazoles and condensed benzimidazoles (Dall'Oglio et al., 2002; Alcade et al., 1991; Goljer et al., 1985). After the study of the behavior of the ^{13}C NMR spectra in the benzimidazole series (Goljer et al., 1985), we are interested to report our contribution in this area by using NMR spectroscopy for the elucidation of carbon13 chemical shifts of these benzimidazole derivatives. We have studied the influence of the substituents on the ^{13}C NMR spectra of these compounds. The complete assignment of the resonances of the ^{13}C NMR spectra of the benzimidazole derivatives was carried out by selective decoupling, NOE, and H, C-COSY experiments (see Figs. 1 and 2).

3. Results and discussion

Tables 1 and 2 give the ^{1}H and ^{13}C NMR data, respectively; of **1a**, **1b**, **2a** and **2b**.

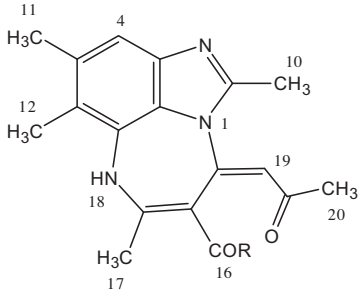
The benzimidazole presents a rapid tautomerism which does not allow to obtain all expected signals in the ^{13}C NMR spectra in the case of substituted benzimidazoles by heterocycles(El Kihel et al., 2005).

This phenomenon was not observed for the open chain intermediates **1a** and **1b** or the condensed benzimidazoles **2a** and **2b**, the ^{13}C NMR spectra of these compounds present all the expected signals.



1a: R= CH_3

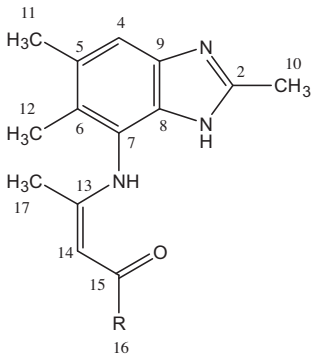
1b: R= OEt



2a: R= CH_3

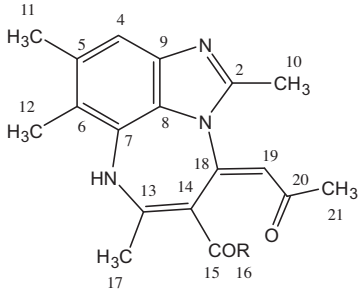
2b: R= OEt

Figure 1 The numbering of the compunds for the ^{1}HNMR assignments.



1a: R= CH_3

1b: R= OEt



2a: R= CH_3

2b: R= OEt

Figure 2 The numbering of the compounds for the ^{13}CNMR assignments.

Table 1 ^{1}H NMR data of the studied compounds.

Proton	Compounds			
	1a	**1b**	**2a**	**2b**
H1	10.19(br s, cyclic NH)	9.99(br s, cyclic NH)		
H4	7.21(s)	7.22(s)	7.36(s)	7.43(s)
H10	2.44(s, CH_3)	2.45(s, CH_3)	2.54(s, CH_3)	2.45(s, CH_3)
H11	2.31(s, CH_3)	2.33(s, CH_3)	2.42(s, CH_3)	2.37(s, CH_3)
H12	2.00(s, CH_3)	2.10(s, CH_3)	1.95(s, CH_3)	1.67(s, CH_3)
H14	5.25(s, olefinic H)	4.69(s, olefinic H)		
H16	1.87(s, CH_3)	1.22(t, CH_3), 4.07(q, CH_2)	1.79(s, CH_3)	1.24(t, CH_3) 4.21(q, CH_2)
H17	2.13(s, CH_3)	2.16(s, CH_3)	2.37(s, CH_3)	1.95(s, CH_3)
H18	12.23(s, NH)	12.32(s, NH)	15.81(s, NH)	12.54(s, NH)
H19			6.20(s, olefinic H)	6.28(s, olefinic H)
H21			1.80(s, CH_3)	1.69(s, CH_3)

Table 2 ^{13}C NMR data of the studied compounds.

Carbon	Compounds chemical shifts (ppm)			
	1a	**1b**	**2a**	**2b**
C2	150.8	159.6	145.2	146.7
C4	110.2	110.2	99.7	112.9
C5	129.8	126.4	132.3	131.1
C6	124.8	117.2	126.8	125.9
C7	130.1	130.1	134.3	133.6
C8	125.6	120.8	128.4	126.1
C9	147.5	150.5	139.1	138.0
C10	14.5	20.6	14.4	14.4
C11	20.5	19.5	18.2	17.1
C12	13.8	14.5	13.3	13.9
C13	162.7	161.6	147.3	149.8
C14	95.8	83.0	124.7	123.5
C15	194.4	169.7	204.1	166.8
C16	38.5	18.3, 57.8	20.1	13.1, 60.7
C17	28.7	48.6	19.2	19.6
C18			154.1	152.6
C19			105.1	116.6
C20			173.3	174.1
C21			20.3	20.3

For the condensed benzimidazoles as imidazobenzodiazepines, we have studied the chemical shifts of vinyl and carbonyl group in order to see the effect of conjugated system.

For the ^{13}C NMR spectra of compounds **2a** and **2b**, the conjugated system induces a systematic shielding of the carbonyl group in position 20 (δ = 173.3 ppm for compound **2a** and δ = 174.1 ppm for compound **2b**) by comparison of the chemical shifts of the carbonyl group in position 15 (δ = 194.4 ppm for compound **1a** and δ = 204.1 ppm for compound **2a**) while the same observation applies to the carbonyl group of ester with less shielding (δ = 169.7 ppm for compound **1b**, δ = 166.8 ppm for compound **2b**). We also noted the deshielding of vinyl group CH in compounds **2a** and **2b** (δ = 105.1 ppm for compound **2a** and δ = 116.6 ppm for compound **2b**) by comparison of that in compounds **1a** and **1b** (δ = 95.8 ppm for compound **1a** and δ = 83.0 ppm for compound **1b**).

4. Experimental section

All compounds were characterized by their ^{1}H NMR and ^{13}C NMR spectra as well as by microanalysis or HRMS spectra. NMR spectra were recorded on Bruker ARX 200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C) spectrometer (Ω-ppm/TMS, J-Hz); for ^{13}C NMR, the multiplicities were determined through DEPT.

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