

**¹³C-NMR AS USEFULL TOOL FOR UNAMBIGUOUS IDENTIFICATION
OF RING SUBSTITUTED N₁₍₂₎₍₃₎-ALKYLBENZOTRIAZOLE ISOMERS**

Antonio Carta^{a*}, Paolo Sanna^a, Giuseppe Paglietti^a, and Fabio Sparatore^b

^aDipartimento Farmaco-Chimico-Tossicologico, University of Sassari, Via Muroni 23, 07100 Sassari, Italy

^bDipartimento di Scienze Farmaceutiche, University of Genova, Viale Benedetto XV 3, 16121 Genova, Italy

Abstract - Analysis of the chemical shifts of C-3a and C-7a angular atoms in the benzotriazoles bearing a substituent on the ring and an alkyl group on the nitrogen position of the triazole moiety proved to be a good tool for identification of the different N-alkyl isomers.

The use of one- and two-dimensional ¹H-NMR techniques for identification of the benzotriazoles and their derivatives has been scarcely employed.^{1,2} However, the results obtained were not very satisfactory whereas it was necessary to identify unambiguously the isomers formed by alkylation in positions 1 and 3 once the heterocycle is ring-substituted in one fixed position, while the products of alkylation on position 2 are usually well characterised owing to their insolubility in acidic medium. Katritzky *et al.* in an investigation on lithiation of 1- and 2-alkylbenzotriazoles, followed by subsequent reactions with iodine and methyl iodide, reported that the lithiation mainly occurs at three positions in the benzene ring with respect to 1-alkylbenzotriazole where the 1,4-disubstituted isomer was prevailing over 1,5- and 1,7-ones, while 2-alkylbenzotriazoles did not undergo ring substitution.² These authors established the precise structures for these isomers by a series of NMR experiments. From the examination of the ¹³C-NMR data reported,² we were able to observe that the chemical shifts assigned to the angular quaternary carbon atoms C-3a and C-7a fall in different regions either they are close to the ring substituent or not. This fact prompted us to investigate if these recurring differences were maintained in both ring and N₁₍₂₎₍₃₎ disubstituted benzotriazoles of structure (**I**, **II** and **III**) of Figure 1 and, if so, a simple method based on ¹³C-NMR spectra could be envisaged to distinguish unambiguously the different isomers. A survey of the literature in this field³⁻⁵ has shown that in the simple 1-substituted benzotriazoles the quaternary carbon

C-7a always resonates in the range 131-133 ppm while for the carbon C-3a the chemical shifts assigned are located at lower downfield in the range 145-147 ppm. In the N-2 no ring-substituted isomers the resonances of both C-3a and C-7a were coincident and located at 145-147 ppm thus indicating no difference in the electronegativity of the two adjacent nitrogen atoms. This general behavior is in good agreement with INAPT experiments carried out by Katritzky *et al.* in the case of 4(7)-iodo-1-isopropylbenzotriazole (**I,II***n*) which correlated the *meta*-relationships between hydrogen atoms and the quaternary carbons.² These observations were also in good accordance with the data recently obtained by some of us for a series of N-1 and N-2 arylidenebenzotriazole isomers.⁶ Thus, we have examined the ¹³C-NMR spectroscopic data of compounds (**Ia-i,k-n**; **IIa,b,d-j,m** and **IIIa-i,k-n**) of Figure 1 and Table 1, some of which were deduced from the literature (**I,IIa**; **Ib**, **I,II,III***f*; **I,III***n*),^{1-4,7} while **I,II,III***m* were not known and prepared as intermediates for another medicinal chemistry project were here used for useful comparison of ring disubstituted benzotriazoles. Compounds (**I,IIb**; **I,IIIc**; **I,II,III***d,e,g-i*; **IIj**; **I,III***k,l*) were known and purposely reprepared according to the data of the literature.⁸⁻¹⁶ In this context we have taken into account the different nature of both the ring substituent (electron-releasing and -withdrawing groups) and the alkyl groups attached to the nitrogen in order to discover which influence they may experience upon the above mentioned angular carbon atoms. In Table 1 we have reported the chemical shift values of C-3a and C-7a grouped by type of isomer as well as that of the carbon atom in the side chain attached to nitrogen according to an order of increasing ring-electronreleasing substituent (CH₃, NH₂) and of decreasing ring-electronwithdrawing substituent (NO₂, CF₃, Cl, I). Examination of the data in Table 1 shows that these are in good accordance with those reported by Katritzky *et al.*⁵ and Milata *et al.*^{17,18} for similar structures. In fact, the resonances of C-7a in the isomers (**Ia-f**), which bear either various substituents on N₁-triazole and H or an electrondonating substituent on the benzene moiety, fall at a higher field (124-133 ppm) than those of C-3a (145-148 ppm), and C-7a and C-3a in the corresponding isomers (**IIa,b,d-f**) (140-147 ppm) and (**IIIc-f**) (133-144 ppm). Conversely, the chemical shift of C-7a in compounds (**Ig-i,k-n**) (133-136 ppm), having an electronwithdrawing substituent, fall at a lower downfield than those of C-7a in the corresponding isomers (**III**) (131-133 ppm), but at a higher field in comparison with C-3a of all isomers (142-147 ppm) and C-7a of the isomers (**II**) (144-146 ppm).

The large list of ¹³C-NMR spectra recorded by us, supports the suggested hypothesis that the range of the chemical shift values of C-3a and C-7a is well associated to each isomer and generally reproducible with small differences due to the electron effect induced by the ring substituent considered. From Table 1 it also appears evident that this analysis is profitable for the identification of the N-2 isomers independently from the nature of the substituent since in each case examined, the chemical shift of both C-3a and C-7a always resonate at a lower downfield than C-7a of the other two isomers. In addition, we have observed that in compounds (**II**) the chemical shift of the first atom carbon in the side chain resonates at a lower downfield in comparison with those of the corresponding isomers (**I**) and (**III**). This is likely due to the

additional deshielding effect of the adjacent nitrogen atoms. These data are well supported by the observations of Milata *et al.* which for similar compounds reported the values of 43.01-43.61 ppm for the isomers of type (II) and 34.29-34.35 for isomers of type (I) and 34.00-34.22 (isomers of type III).¹⁷

This observation furthermore confirms the relationships existing among the basicity of the nitrogen atoms in triazole ring, where in the central atom it decreases owing to the electronwithdrawing effect of the adjacent nitrogen atoms.¹⁹ It also seems interesting to note that the difference in the chemical shift values between C-3a and C-7a atoms ($\Delta = C-3a - C-7a$), in the isomers bearing ring electronreleasing substituents, is **I** > **II** > **III**, whereas in the isomers having electronwithdrawing substituents it is **III** > **I** > **II**. This evidence enables us to suggest that the chemical shifts of C-3a and C-7a are under the influence of the sole *para* electron effect of the substituent in the case of 5- and 6- ring-substituted benzotriazoles.

Most of the reported compounds in Table 1 were previously described and are adequately referenced. In the experimental section we reported full data of ¹³C-NMR not available in literature. Compounds (**I,II,III**m) are new and described in detail in the experimental section. For their preparation we used the sequence of reactions depicted in Scheme 1, starting from the intermediate (**1**) that was obtained through a described procedure purposely modified by us.²⁰ Achievement of the known 3,4-dichloro-1,2-diaminobenzene (**2**)²¹ by catalytic hydrogenation of **1**, allowed us to obtain 4,5-dichlorobenzotriazole (**3**) by ring closure. This was then alkylated with chloroacetonitrile in DMF in the presence of triethylamine to afford **I, II, III**m according to a previously described procedure of ours.⁶

In conclusion this approach seems to offer a good and simple tool for the identification of substituted benzotriazoles.

Compd	R	R ₁ (I)	R ₁ (III)	R ₁ (II)	Ref.
a	Me	H	H	H	3,4
b	CH ₂ CN	H	H	H	6,7
c	CHMeCH ₂ CO ₂ H	5-Me	6-Me	-	8,16
d	Me	5-NH ₂	6-NH ₂	5-NH ₂	9-11
e	CH ₂ CO ₂ Et	5-NH ₂	6-NH ₂	5-NH ₂	12
f	CH=CHCO ₂ Me	5-NH ₂	6-NH ₂	5-NH ₂	1
g	Me	5-NO ₂	6-NO ₂	5-NO ₂	13
h	Et	5-NO ₂	6-NO ₂	5-NO ₂	14
i	CH ₂ CO ₂ Et	5-NO ₂	6-NO ₂	5-NO ₂	15
j	CHMeCH ₂ CO ₂ H	-	-	5-NO ₂	8,16
k	CHMeCH ₂ CO ₂ H	5-CF ₃	6-CF ₃	-	8,16
l	Me	5-CF ₃	6-CF ₃	-	16
m	CH ₂ CN	6,7-Cl ₂	4,5-Cl ₂	4,5-Cl ₂	-
n	CHMe ₂	7-I	4-I	-	2

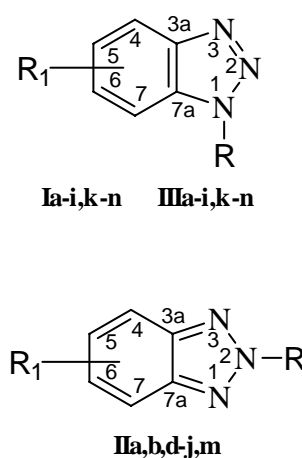
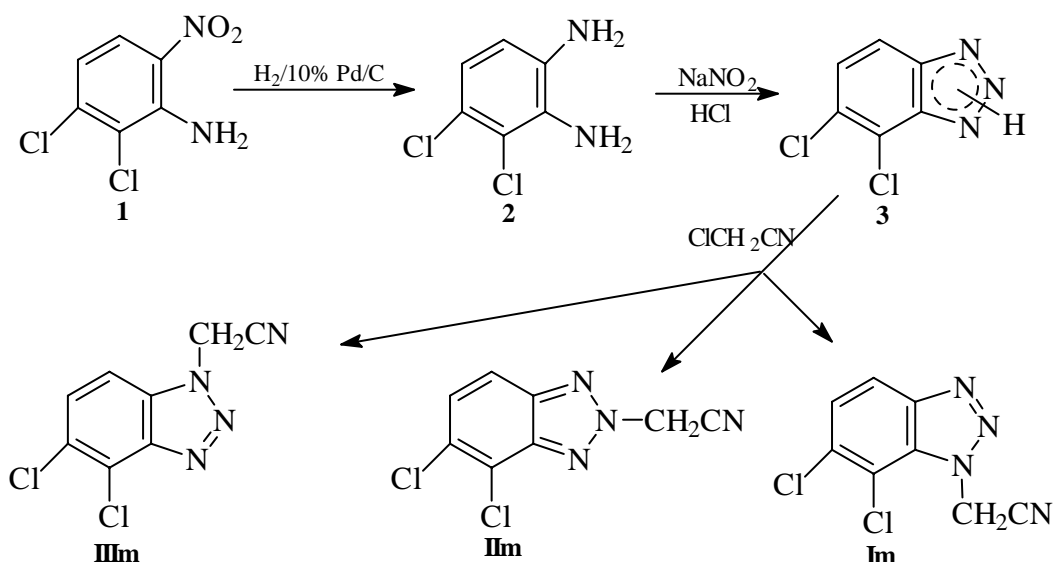


Figure 1. List of examined benzotriazole isomers.

Compd ^{Ref.}	Chemical shifts series I (ppm)			Chemical shifts series III (ppm)			Chemical shifts series II (ppm)		
	C-3a	C-7a	N-C	C-3a	C-7a	N-C	C-3a	C-7a	N-C

a ^{3,4}	(145.5) ³ (145.8) ⁴	(133.1) ³ (133.4) ⁴	(34.1) ^{3,4}	-	-	-	(144.5) ⁴	(144.5) ⁴	(43.2) ⁴
b ⁷	(146.2) ⁷	(132.3) ⁷	(35.7) ⁷	-	-	-	145.1	145.1	43.5
c	145.8	130.9	51.6	144.0	132.8	51.5	-	-	-
d	147.0	127.2	33.9	138.8	135.2	33.3	145.7	139.6	42.4
e	147.3	128.0	48.4	138.7	135.4	48.0	146.3	140.4	56.5
f ¹	148.0	124.1	136.0	138.3	133.6	136.2	147.0	141.1	140.1
g	144.1	136.0	34.7	146.1	132.7	34.9	142.4	145.9	44.1
h	144.1	135.2	43.3	146.2	131.9	43.5	142.1	145.8	52.2
i	145.1	136.1	49.3	148.0	132.8	49.5	143.3	146.6	57.7
j	-	-	-	-	-	-	141.9	145.9	60.6
k	144.2	134.1	52.1	146.3	132.1	52.0	-	-	-
l	144.1	134.9	34.5	146.4	132.8	34.6	-	-	-
m	145.9	134.2	37.4	145.0	132.0	36.1	144.1	144.2	43.7
n ²	146.6	133.0	51.1	147.4	131.1	52.1	-	-	-

Table 1. ¹³C-NMR chemical shifts of C-3a, C-7a and N-C of compounds of series (I, II, III).



Scheme 1

EXPERIMENTAL

Melting points are uncorrected and were taken in open capillaries in a Digital Electrothermal IA9100 melting point apparatus. In brackets are reported the recrystallization solvents. IR spectra were recorded as nujol mulls or film on a Perkin Elmer 781 spectrophotometer and are expressed in cm⁻¹. UV spectra are qualitative and were recorded in nm for ethanol solution with a Perkin-Elmer Lambda 5 spectrophotometer. ¹H-NMR spectra were recorded at 200 MHz using a Varian XL-200 spectrometer, ¹³C-NMR spectra were recorded on the same instrument at 50 MHz. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as internal standard. MS spectra were performed on a combined HP 5790

(GC)-HP 5970 (MS) apparatus. Column chromatography was performed using 70-230 mesh (Merck silica gel 60). The progress of the reactions and the purity of the final compounds were monitored by TLC using Merck F-254 commercial plates. Light petroleum refers to the fraction with bp 40-60°C. Elemental analyses were performed at the Laboratorio di Microanalisi, Dipartimento di Scienze Farmaceutiche, University of Padua-Italy.

Preparation of 4,5-dichlorobenzotriazole (3). A solution of sodium nitrite (0.8 g, 11.6 mmol) in water (4 mL) was added dropwise to a solution of **2** (1.0 g, 5.6 mmol) in 20 mL of 4N aqueous solution of hydrochloric acid (20 mL) cooled with ice bath. After complete addition, the temperature was arisen to rt and stirring continued for an additional 10 h. The solid precipitate was filtered off, thoroughly washed with water and dried, to give **3** (1.02 g, 96 %) of mp 242-244 °C (Me₂CO); IR (nujol): 1650, 1610, 1580 cm⁻¹; UV (EtOH): 286, 216 nm; ¹H-NMR (CDCl₃+DMSO-d₆) δ: 7.75 (d, 1H, *J*=9.0 Hz, H-6), 7.49 (d, 1H, *J*=9.0 Hz, H-5), MS: *m/z* 187 (M⁺). Anal. Calcd for C₆H₃N₃Cl₂: C, 38.33; H, 1.61; N, 22.35; Cl, 37.72. Found: C, 38.50; H, 1.92; N, 22.19; Cl, 38.02.

Preparation of 2-[6,7-dichlorobenzotriazol-1-yl]acetonitrile (Im), 2-[4,5-dichlorobenzotriazol-2-yl]acetonitrile (IIIm), and 2-[4,5-dichlorobenzotriazol-1-yl]acetonitrile (IIIIm). A solution of **3** (0.95 g, 5.0 mmol) and triethylamine (0.73 g, 7.21 mmol) in DMF (5 mL) was stirred at rt for 10 min, added chloroacetonitrile (0.5 g, 6.6 mmol) and then heated at 110 °C for 14 h. After the solution was allowed to cool to rt, the precipitate of triethylamine hydrochloride was filtered off, and the mother liquors evaporated in *vacuo*. The crude oil residue obtained was purified by "flash" chromatography on silica gel, eluting with a mixture of ether-light petroleum 60:40, affording in the order: **IIIm** (0.13 g, 11.3 %) mp 158-159 °C (Et₂O); IR (nujol): 2230 (CN), 1610 cm⁻¹; UV (EtOH): 284, 215 nm; ¹H-NMR (CDCl₃) δ: 7.77 (d, 1H, *J*=9.0 Hz, H-7), 7.51 (d, 1H, *J*=9.0 Hz, H-6), 5.68 (s 2H, CH₂), ¹³C-NMR (CDCl₃) δ: 144.25 (C-7a), 144.10 (C-3a), 131.85 (C-4), 130.17 (C-7), 121.27 (C-5), 117.56 (C-6), 111.64 (CN), 43.67 (CH₂). MS: *m/z* 226 (M⁺). Anal. Calcd for C₈H₄N₄Cl₂: C, 42.32; H, 1.78; N, 24.68; Cl, 31.23. Found: C, 42.41; H, 2.03; N, 24.34; Cl, 31.15; **Im** (0.40 g, 35 %) mp 125-126 °C (Et₂O); IR (nujol): 2300 (CN), 1610 cm⁻¹; UV (EtOH): 284 sh, 270, 263, 222 nm; ¹H-NMR (CDCl₃) δ: 7.96 (d, 1H, *J*=8.6 Hz, H-4), 7.54 (d, 1H, *J*=8.6 Hz, H-5), 5.87 (s 2H, CH₂), ¹³C-NMR (CDCl₃) δ: 145.87 (C-3a), 134.22 (C-7a), 130.72 (C-6), 127.52 (C-4), 119.52 (C-5), 114.22 (C-7), 113.06 (CN), 37.41 (CH₂). MS: *m/z* 226 (M⁺). Anal. Calcd for C₈H₄N₄Cl₂: C, 42.32; H, 1.78; N, 24.68; Cl, 31.23. Found: C, 42.19; H, 1.97; N, 24.49; Cl, 31.08. **IIIIm** (0.43 g, 37.4 %) mp 152-153 °C (Et₂O); IR (nujol): 2260 (CN), 1620 cm⁻¹; UV (EtOH): 296, 268, 261, 217 nm; ¹H-NMR (CDCl₃) δ: 7.69 (d, 1H, *J*=9.2 Hz, H-6), 7.55 (d, 1H, *J*=9.2 Hz, H-7), 5.63 (s, 2H, CH₂), ¹³C-NMR (CDCl₃) δ: 145.03 (C-3a), 132.03 (C-7a), 130.92 (C-6), 129.66 (C-4), 124.61 (C-

5), 111.78 (CN), 107.76 (C-7), 36.15 (CH₂). MS: *m/z* 226 (M⁺). Anal. Calcd for C₈H₄N₄Cl₂: C, 42.32; H, 1.78; N, 24.68; Cl, 31.23. Found: C, 42.51; H, 1.64; N, 25.01; Cl, 31.49.

¹³C-NMR spectroscopic data not reported in the literature of compounds (I, IIIc-e,g-i,k-m; and IIb,d-j,m).

IIb (CDCl₃) δ: 145.06 (C-3a + C-7a), 127.01 (C-5 + C-6), 118.16 (C-4 + C-7), 112.26 (CN), 43.48 (CH₂).

Ic (DMSO-d₆) δ: 171.45 (COO), 145.81 (C-3a), 133.49 (C-5), 130.87 (C-7a), 128.07 (C-6), 117.87 (C-4), 110.39 (C-7), 51.63 (N-CH), 40.12 (CH₂), 20.76 (CH₃).

IIIc (DMSO-d₆) δ: 171.52 (COO), 143.97 (C-3a), 137.23 (C-6), 132.78 (C-7a), 126.14 (C-5), 118.67 (C-4), 109.81 (C-7), 51.51 (N-CH), 40.11 (CH₂), 20.80 (CH₃).

Id (DMSO-d₆) δ: 147.00 (C-3a), 145.83 (C-5), 127.24 (C-7a), 119.06 (C-6), 110.34 (C-7), 97.66 (C-4), 33.92 (CH₃).

IIId (DMSO-d₆) δ: 148.82 (C-6), 138.82 (C-3a), 135.24 (C-7a), 119.25 (C-4), 115.55 (C-5), 88.49 (C-7), 33.29 (CH₃).

IIId (CDCl₃) δ: 145.74 (C-3a), 144.96 (C-5), 139.65 (C-7a), 120.14 (C-6), 118.18 (C-7), 96.32 (C-4), 42.41 (CH₃).

Ie (CDCl₃) δ: 166.41 (COO), 147.29 (C-3a), 143.74 (C-5), 128.03 (C-7a), 119.76 (C-6), 109.54 (C-7), 101.15 (C-4), 62.05 (O-CH₂), 48.37 (N-CH₂), 13.87 (CH₃).

IIIe (DMSO-d₆) δ: 167.49 (COO), 149.19 (C-6), 138.69 (C-3a), 135.40 (C-7a), 119.40 (C-4), 115.56 (C-5), 88.76 (C-7), 61.37 (O-CH₂), 48.03 (N-CH₂), 13.99 (CH₃).

IIe (CDCl₃) δ: 166.43 (COO), 146.26 (C-3a), 145.41 (C-5), 140.36 (C-7a), 121.22 (C-6), 118.73 (C-7), 96.40 (C-4), 62.13 (O-CH₂), 56.52 (N-CH₂), 13.92 (CH₃).

Ig (DMSO-d₆) δ: 144.14 (C-3a), 143.89 (C-5), 136.01 (C-7a), 121.79 (C-4), 116.17 (C-6), 111.85 (C-7), 34.66 (CH₃).

IIIg (DMSO-d₆) δ: 147.12 (C-6), 146.08 (C-3a), 132.72 (C-7a), 120.14 (C-4), 118.54 (C-5), 108.61 (C-7), 34.97 (CH₃).

IIg (DMSO-d₆) δ: 145.99 (C-5), 145.87 (C-7a), 142.36 (C-3a), 120.45 (C-6), 119.24 (C-7), 115.79 (C-4), 44.12 (CH₃).

Ih (DMSO-d₆) δ: 144.17 (C-5), 144.07 (C-3a), 135.22 (C-7a), 121.78 (C-4), 116.27 (C-6), 111.76 (C-7), 43.33 (CH₂), 14.71 (CH₃).

IIIh (DMSO-d₆) δ: 147.23 (C-6), 146.92 (C-3a), 131.91 (C-7a), 120.25 (C-4), 118.64 (C-5), 108.50 (C-7), 43.47 (CH₂), 14.94 (CH₃).

IIIh (DMSO- d_6) δ : 145.79 (C-7a), 145.75 (C-5), 142.10 (C-3a), 120.31 (C-6), 119.30 (C-7), 115.80 (C-4), 52.23 (CH₂), 14.57 (CH₃).

IIi (CDCl₃) δ : 165.64 (COO), 145.06 (C-3a), 144.78 (C-5), 136.06 (C-7a), 122.81 (C-4), 117.21 (C-6), 110.24 (C-7), 62.33 (O-CH₂), 49.33 (N-CH₂), 13.93 (CH₃).

IIIi (CDCl₃) δ : 165.68 (COO), 148.02 (C-3a), 147.14 (C-6), 132.77 (C-7a), 120.99 (C-4), 118.99 (C-5), 106.91 (C-7), 62.66 (O-CH₂), 49.45 (N-CH₂), 13.92 (CH₃).

IIIi (CDCl₃) δ : 165.28 (COO), 146.70 (C-5), 146.63 (C-7a), 143.28 (C-3a), 120.33 (C-6), 119.52 (C-7), 116.32 (C-4), 62.63 (O-CH₂), 57.70 (N-CH₂), 13.92 (CH₃).

IIj (DMSO- d_6) δ : 171.08 (COO), 145.94 (C-7a), 145.51 (C-5), 141.90 (C-3a), 120.46 (C-6), 119.49 (C-7), 116.01 (C-4), 60.56 (N-CH), 39.84 (CH₂), 21.09 (CH₃).

IIk (DMSO- d_6) δ : 171.37 (COO), 144.20 (C-3a), 134.11 (C-7a), 124.95 (C-5, J_{C-F} = 4 Hz), 124.33 (CF₃, J_{C-F} = 270 Hz), 123.36 (C-4, J_{C-F} = 3 Hz), 117.53 (C-6, J_{C-F} = 4 Hz), 112.76 (C-7), 52.09 (N-CH), 40.14 (CH₂), 20.74 (CH₃).

IIIk (DMSO- d_6) δ : 171.54 (COO), 146.32 (C-3a), 132.07 (C-7a), 127.53 (C-6, J_{C-F} = 32 Hz), 121.34 (CF₃, J_{C-F} = 270 Hz), 120.66 (C-4), 120.34 (C-5, J_{C-F} = 3 Hz), 110.03 (C-7, J_{C-F} = 4 Hz), 52.00 (N-CH), 40.23 (CH₂), 20.94 (CH₃).

II (DMSO- d_6) δ : 144.15 (C-3a), 134.94 (C-7a), 124.76 (C-5, J_{C-F} = 32 Hz), 124.24 (CF₃, J_{C-F} = 270 Hz), 123.38 (C-4, J_{C-F} = 3 Hz), 117.41 (C-6, J_{C-F} = 4 Hz), 112.44 (C-7), 34.49 (CH₃).

III (DMSO- d_6) δ : 146.35 (C-3a), 132.77 (C-7a), 127.36 (C-6, J_{C-F} = 32 Hz), 124.28 (CF₃, J_{C-F} = 270 Hz), 120.52 (C-4), 120.13 (C-5, J_{C-F} = 3 Hz), 109.75 (C-7, J_{C-F} = 4 Hz), 34.64 (CH₃).

REFERENCES

1. A. Carta, P. Sanna, and H. Molinari, *Heterocycles*, 1997, **45**, 1391.
2. A. R. Katritzky, D. C. Oniciu, L. Serdyuk, and I. Ghiviriga, *J. Org. Chem.*, 1995, **60**, 1244.
3. R. Faure and E. J. Vincent, *Heterocycles*, 1983, **20**, 1713.
4. A. R. Katritzky, I. Ghiviriga, and D. J. Cundy, *Heterocycles*, 1994, **38**, 1041.
5. A. R. Katritzky, G. F. Zhang, W. Q. Fan, J. Wu, and J. Pernak, *J. Phys. Org. Chem.*, 1993, **6**, 567.
6. P. Sanna, A. Carta, and M. E. Rahbar Nikookar, *Eur. J. Med. Chem.*, 2000, **35**, 535.
7. A. R. Katritzky, S. Rachwal, K. C. Caster, F. Mahni, K. W. Law, and O. Rubio, *J. Chem. Soc., Perkin Trans. I*, 1987, 781.
8. G. Paglietti and F. Sparatore, *Il Farmaco, Ed. Sci.*, 1972, **27**, 380.
9. M. Kamel, S. Sherif, and M. M. Kamel, *Tetrahedron*, 1964, **20**, 211.
10. M. Kamel, M. I. Ali, and M. M. Kamel, *Liebigs Ann. Chem.*, 1970, **733**, 115.
11. J. Pinnow and E. Koch, *Ber.*, 1897, **30**, 2850.

12. M. E. Rahbar Nikookar, "Tesi di Dottorato in Scienze Farmaceutiche XIII Ciclo", Università di Genova (Italy), 2000, 31.
13. G. Paglietti and F. Sparatore, *Annali di Chimica*, 1972, **62**, 128.
14. P. Sanna, A. Carta, G. Paglietti, A. Bacchi, and G. Pelizzi, *J. Heterocycl. Chem.*, 1997, **34**, 97.
15. C. W. Schellhammer, J. Schroeder, and N. Joop, *Tetrahedron*, 1970, **26**, 497.
16. G. Paglietti, P. Sanna, A. Carta, F. Sparatore, I. Vazzana, A. Peana, and M. Satta, *Il Farmaco*, 1994, **49**, 693.
17. V. Milata, D. Ilavsky, and I. Goljer, *Collect. Czech. Chem. Commun.*, 1989, **54**, 713.
18. V. Bobosik, V. Milata, D. Ilavsky, and I. Goljer, *Collect. Czech. Chem. Commun.*, 1992, **57**, 397.
19. A. Wamhoff, "Comprehensive Heterocyclic Chemistry", Vol. 5, ed. by A. R. Katritzky, C. W. Rees, and K. T. Potts, Pergamon, England, **1984**, pp. 669-732.
20. P. Sanna, A. Carta, and G. Paglietti, *Heterocycles*, 2000, **53**, 423.
21. S. Saluja, R. Zou, J. C. Drach, and L. B. Townsend, *J. Med. Chem.*, 1996, **39**, 881.