STRUCTURAL ELUCIDATION OF ISOMERIC METHYL (*E*)-3-[5-AMINOBENZOTRIAZOL-1(2)(3)-YL]PROPENOATES BY NMR SPECTROSCOPY

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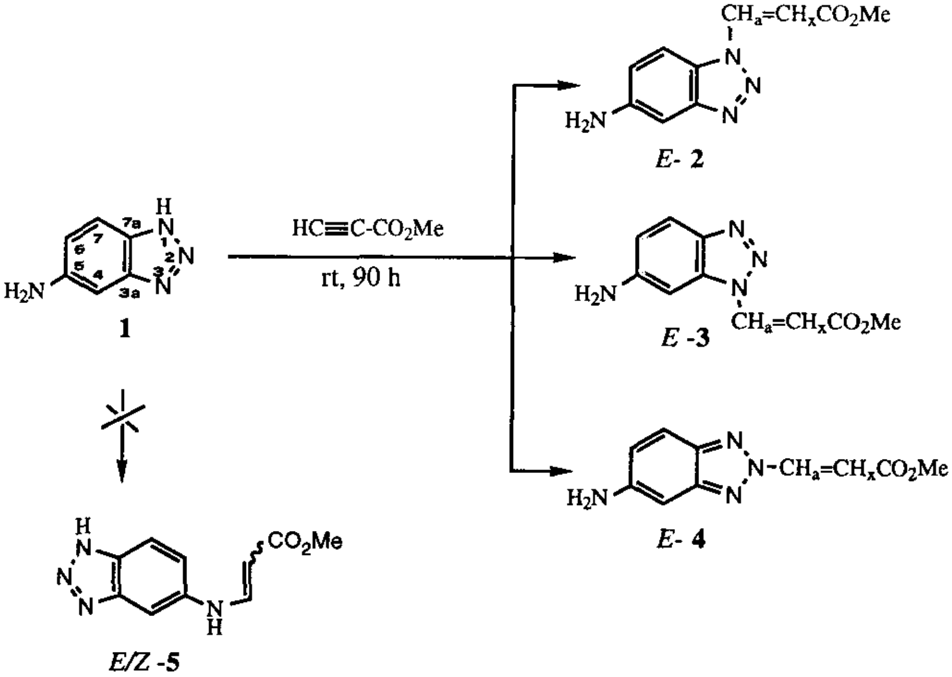
Abstract- Revised attribution of the structure to three isomers of methyl (*E*)-3-[5-aminobenzotriazol-1(2)(3)-yl]propenoate ((*E*)-**2**, **3** and **4**), using combined experiments of mono- and two-dimensional NMR spectroscopy, is reported.

In a previous paper we reported that the reaction of 5-aminobenzotriazole (**1**) with methyl propynoate gave, according to Michael's reaction, a mixture of three isomers of the methyl (*E*)-3-[5-aminobenzotriazol-1(2)(3)-yl]propenoate (*E*)-**2**, **3** and **4**, instead of the expected addition product (**5**), necessary for an other project.[1]



Scheme 1

Attribution of the structure to each isomer was achieved comparing our spectroscopic data (UV, IR, ^{1}H- and ^{13}C-NMR) with those reported in the literarure for similar cases.[2-4] In particular, the overall data allowed to distinguish between the 1- and 3-monosubstituted isomers from the 2-substituted one, while the difference between 1- and 3-substituted benzotriazoles are negligible and uncertainty may arise in the exact attribution of the structure to each single isomer. This is the case of compounds ((*E*)-**2**, (*E*)-**3** and (*E*)-**4**), the NMR data of which, reported in Table 1, clearly show how the overlapping of both proton and carbon signals prevent any exact assignment.

Table 1. ^{1}H- and ^{13}C-NMR chemical shifts ranges of compounds (*E*)-**2,3,4**.

^{1}H-NMR	δ Range	Multiplicity	J (Hz)	^{13}C-NMR	δ Range
H_a	8.2-8.5	d	14-14.2	C=O	165.1-166.1
H-7	7.5-7.8	d	9-9.4	C-5	147.5-151.4
H-4	6.6-7.2	d	1.8-2	C-H_a	136.0-140.0
H-6	6.8-7.1	dd	9-9.4 and 1.8-2	C-7	111.8-120.5
H_x	6.4-6.6	d	14-14.2	C-6	116.0-125.2
NH_2	5.5-6.0	s	-	C-H_x	104.9-108.8
CH_3	3.7-3.8	s	-	C-4	90.7-98.7
				CH_3	51.8-51.9

A definition of the correct structure for this type of compounds was necessary owing to their extensive use as intermediates in building up molecules of biological interest.[5] In this contest we have used simple two-dimensional nmr methods for solving the above problems. Thus, we have found that ^{13}C-^{1}H heteronuclear nmr experiments (Figure 1) could be an useful method to correlate each proton, of each single isomer, with their scalary coupled carbon atoms.[6] Of course C-3a and C-7a, being quaternary carbons, do not exhibit such correlation.

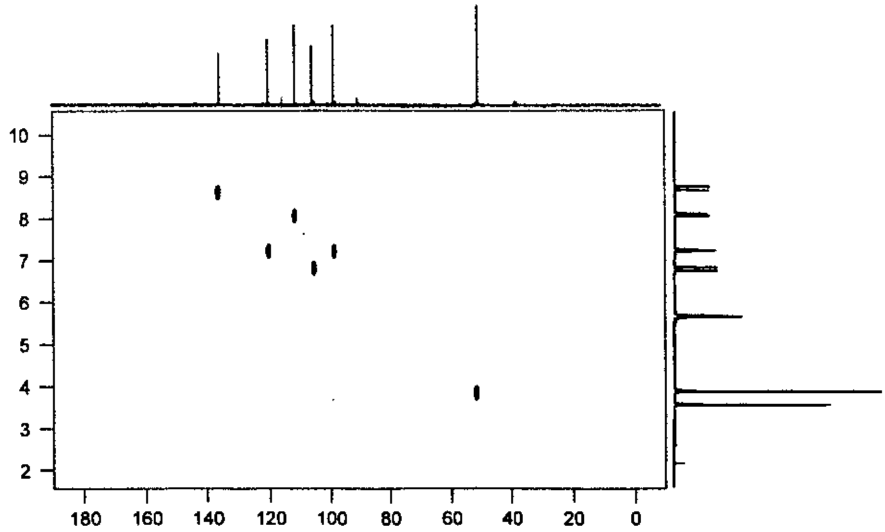


Figure 1. ^{13}C-^{1}H Heteronuclear NMR for compound ((*E*)-**2**).

In addition NOESY experiments[7] were used to check if H-7 or H-4 protons were closed in space to H_a and H_x protons, beloging to the side chain on N-1 or N-3 atoms, as in the case of isomers ((*E*)-**2**) and ((*E*)-**3**). Comparison of ^{1}H-NOESY data for compounds ((*E*)-**2**) and ((*E*)-**3**) allowed us to establish that when irradiation at δ 7.9 take place a NOE between the doublet of H-7 with those of H_a (δ 8.5) and H_x (δ 6.6) occurred. This result was pertinent to the structure of the isomer ((*E*)-**2**) (Figure 2). Instead the Figure 3 shows an NOE between the doublets of the H_a (δ 8.4) and H_x (δ 6.4) protons with the singlet of the H-4 at δ 6.9, thus indicating unambiguously the alternative structure for (*E*)-**3**.

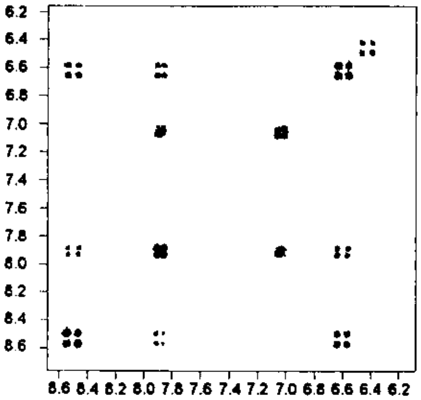


Figure 2. ^{1}H-NOESY for compound ((*E*)-**2**).

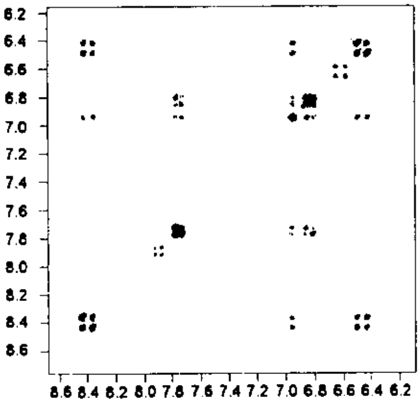


Figure 3. ^{1}H-NOESY for compound ((*E*)-**3**).

Exact assignment of the quaternary carbon C-3a and C-7a could be then deduced by evidentiation of $^3J_{H\text{-}C}$ using "Gate decoupling"[8] and "Hetcor long range"[6] tecniques. A fully coupled ^{13}C-NMR spectrum of (*E*)-**2** exhibited a signal for C-7a (δ 124.1) as *ddd*, thus indicating the long range coupling with H-6, H-4 and H_a (Figure 4a). Selective decoupling of H_a signal (δ 8.5) produced a simplified *dd* due to coupling between C-7a with both H-6 and H-4 protons (Figure 4b), thus confirming that, the alkenoic chain was attached to the N-1 atom. Conversely, the isomer ((*E*)-**3**) was deduced by difference.

Another support to this conclusion came from the ^{1}H-NOESY spectrum of compound ((*E*)-**4**) (Figure 5) where no cross peaks were observed between H_a and H_x with H-4 and H-7 protons respectively, in agreement with their long distance.

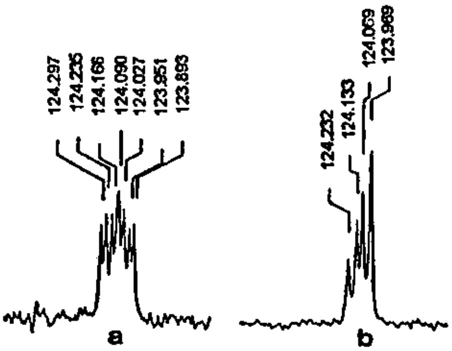


Figure 4. a) Fully coupled ^{13}C-NMR for C-7a signal of (*E*)-**2**; b) selective decoupling of H_a signal for (*E*)-**2**.

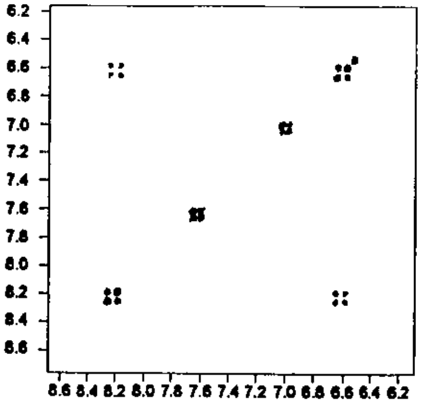


Figure 5. ^{1}H-NOESY for compound ((*E*)-**4**).

Figure 6 showed the conformation at lowest energy related to both compounds ((*E*)-**2**) and ((*E*)-**3**), whereas Table 2 described the distances, dihedral angles and energies of three conformers at the highest stability of the same compounds.

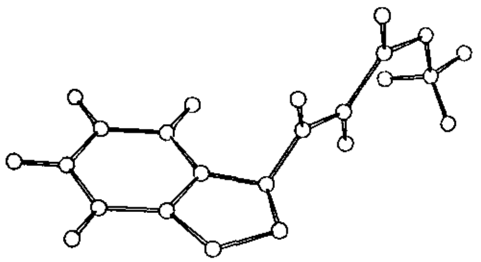


Figure 6. Lowest energy conformation for compounds ((*E*)-**2**) and ((*E*)-**3**).

Table 2. Data of the calculations for three conformers of (*E*)-**2** or (*E*)-**3**.

Conformer	Distance H_4/H_a or H_7/H_a (A)	Distance H_4/H_x or H_7/H_x (A)	Dihedral angle ϕ C_{3a}-N_3-CH_a-H_x C_{7a}-N_1-CH_a-H_x	Energy kcal/mole
1	3.15	3.92	-122°	25.12
2	3.28	3.55	51°	24.78
3	3.31	3.31	60°	24.65

On the basis of these results, the data of ^{1}H- and ^{13}C-NMR spectra previously assigned to isomers ((*E*)-**2**, **3** and **4**),[1] must be corrected as reported in Table 3.

Table 3. New values of proton and carbon chemical shifts of the compounds ((*E*)-**2**, (*E*)-**3** and (*E*)-**4**).

Compoud	^{1}H-NMR (DMSO-d_6) δ ppm (J in Hz)	^{13}C-NMR (DMSO-d_6) δ ppm
(*E*)-**2**	8.51 (1H, d, J = 14.2, H_a), 7.90 (1H, d, J = 9, H-7), 7.06 (1H, d, J = 2, H-4), 7.04 (1H, dd, J = 9 and 2, H-6), 6.62 (1H, d, J = 14.2, H_x), 5.51 (2H, s, NH_2), 3.76 (3H, s, CH_3)	166.06 (s, CO), 147.95 (s, C-3a), 147.53 (s, C-5), 135.98 (d, C-H_a), 124.09 (s, C-7a), 120.24 (d, C-6), 111.76 (d, C-7), 105.70 (d, C-H_x), 98.56 (d, C-4), 51.78 (q, CH_3)
(*E*)-**3**	8.40 (1H, d, J = 14.2, H_a), 7.74 (1H, d, J = 9, H-7), 6.94 (1H, d, J = 1.8, H-4), 6.83 (1H, dd, J = 9 and 1.8, H-6), 6.45 (1H, d, J = 14.2, H_x), 6.03 (2H, s, NH_2), 3.75 (3H, s, CH_3)	166.14 (s, CO), 151.40 (s, C-5), 138.83 (s, C-7a), 136.15 (d, C-H_a), 133.62 (s, C-3a), 120.55 (d, C-7), 116.02 (d, C-6), 104.87 (d, C-H_x), 90.71 (d, C-4), 51.79 (q, CH_3)
(*E*)-**4**	8.23 (1H, d, J = 14, H_a), 7.65 (1H, d, J = 9.4, H-7), 7.04 (1H, dd, J = 9.4 and 2, H-6), 6.64 (1H, d, J = 14, H_x), 6.56 (1H, d, J = 2, H-4), 5.95 (2H, s, NH_2), 3.75 (3H, s, CH_3)	165.62 (s, CO), 149.55 (s, C-5), 147.80 (s, C-3a), 141.13 (s, C-7a), 140.05 (d, C-H_a), 125.15 (d, C-6), 118.69 (d, C-7), 108.80 (d, C-H_x), 90.55 (d, C-4), 51.95 (q, CH_3)

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 with tetramethylsilane as internal standard on a Varian XL-200 spectrometer at 200 MHz and 50 MHz respectively. Mixing time employed for NOESY was of 0.55*s* , whereas for two-dimensional Hetcor we used an J average of 140 and 7 Hz. Molecular mechanic calculations were performed by MM2 computation, using the Discover packed from Biosjm.

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