

Influence of Some Thia- or Azasubstituted Butyric Acid Derivatives on the Chemical Shift of the Benzene Ring Carbon Atoms

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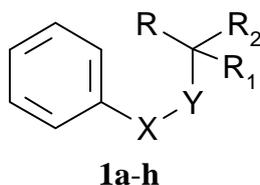
Abstract: Eight thia- or azasubstituted butyric acid derivatives were prepared and the influence of these substituents on the chemical shifts of the benzene ring carbon atoms was studied.

Keywords: 4-phenyl-3-thiabutyric acid derivatives, 4-phenyl-3-azabutyric acid derivatives, substituent chemical shifts.

Introduction

For the synthesis of derivatives of (iso)thiochromanone and isoquinolone it was necessary to prepare eight appropriately substituted 4-phenyl-3-(or 4-)thia(or aza)butyric acids and derivatives **1**. We now report a study of the influence of these substituents on the chemical shifts of the benzene ring carbon atoms of the compounds prepared (Table 1).

Table 1.



No.	X	Y	R ₁	R ₂	R	No.	X	Y	R ₁	R ₂	R
1a	CH ₂	S	H	H	COOH	1e	CH ₂	NH	- (CH ₂) ₄ -		CN
1b	S	CH ₂	H	H	COOH	1f	CH ₂	NH	- (CH ₂) ₄ -		COOH
1c	CH ₂	S	H	H	COOMe	1g	CH ₂	NMe	- (CH ₂) ₄ -		CN
1d	S	CH ₂	H	H	COOMe	1h	CH ₂	NMe	- (CH ₂) ₄ -		COOH

Results and Discussion

Chemical shifts of all of the compounds studied were assigned on the basis of comparisons between the experimental values acquired from recorded spectra and those calculated using the following programs: ACD / CNMR ver. 1.1 [6], CS Chem Draw Pro, ver. 4.5 [7] and ChemWindow3, ver. 3.0.0 with C13-module [8], respectively. We obtained a good agreement between the measured chemical shifts values and those calculated using all three programs.

Chemical shifts (δ) and the substituent chemical shift ($\Delta \delta$) of all of the compounds with heteroatoms in the β -position are in the same range for all compounds studied. The compounds with the heteroatom in the α -position (**1b,d**) have the ipso-carbon less shifted than the analogues having the heteroatom in the β -position (**1a,1c,1e-1h**). Substituent chemical shifts of meta-carbon atoms of the benzene ring of compounds **1a, 1b** and **1d** have positive values unlike all the other compounds: **1c, 1e-1h**.

The influence of the studied substituents on the chemical shifts of the benzene ring carbon atoms can be compared, for example with CH₂SMe (**1a, 1c**), SMe (**1b, 1d**) or CH₂NHCHMe₂, CH₂NMeCH₂Ph substituents [9] which show good agreement with model compounds (see Table 2). Perhaps $\Delta \delta$ for C_{ipso} are slight reduced for all compounds by about 2 ppm and **1b, 1d** have positive values for C_{ortho} in comparison with the compounds bearing the SMe substituents, but this also depends on the solvents used [9].

Table 2. Chemical shifts (δ , in ppm) and substituent chemical shifts ($\Delta \delta$) of the benzene ring carbon atoms of 4-phenyl-3-(or 4-)thia(or aza)butyric acid derivatives.

- X - Y - CR ₁ R ₂ R*		C _{ipso}	C _{orto}	C _{meta}	C _{para}	Other signals
-CH ₂ -S-CH ₂ -COOH, 1a	δ	136.8	129.2	128.6	127.4	176.8, 36.3, 31.9
	$\Delta \delta$	+8.3	+0.7	+0.1	-1.1	
-S-CH ₂ CH ₂ -COOH, 1b	δ	135.0	130.1	129.0	126.6	177.1, 34.4, 30.9
	$\Delta \delta$	+6.5	+1.6	+0.5	-1.9	
-CH ₂ -S-CH ₂ -COOMe, 1c	δ	137.0	128.9	128.3	127.0	170.5, 52.0, 36.1, 31.8
	$\Delta \delta$	+8.5	+0.4	-0.2	-1.5	
-S-CH ₂ CH ₂ -COOMe, 1d	δ	135.0	129.8	128.8	126.3	171.8, 51.5, 33.9, 28.7
	$\Delta \delta$	+6.5	+1.3	+0.3	-2.2	
-CH ₂ -NH-C(CH ₂) ₄ CN, 1e	δ	139.2	128.5	128.3	127.3	122.9, 61.2, 50.2, 39.0, 23.5
	$\Delta \delta$	+10.7	0	-0.2	-1.2	
-CH ₂ -NH-C(CH ₂) ₄ COOH, 1f	δ	140.0	128.4	127.7	127.0	179.5, 70.0, 48.4, 35.8, 24.2
	$\Delta \delta$	+11.5	-0.1	-0.8	-1.5	
-CH ₂ -NMe-C(CH ₂) ₄ CN, 1g	δ	138.3	128.5	128.2	126.8	120.2, 68.8, 58.4, 38.5, 37.9, 23.2
	$\Delta \delta$	+9.8	0	-0.3	-1.7	
-CH ₂ -NMe-C(CH ₂) ₄ COOH, 1h ^a	δ	140.0	128.3	128.2	126.7	176.6, 74.7, 56.7, 36.0, 32.1, 24.8
	$\Delta \delta$	+11.5	-0.2	-0.3	-1.8	

* δ (Benzene) = 128.5 ppm, δ (Chloroform) = 77.0 ppm, ^ain DMSO-d₆, δ (DMSO) = 39.0 ppm

Experimental

General

The synthesis of thiabutyric acid derivatives was described long ago [1-3] but their ¹³C NMR spectra have not been published until now. In the case of 3-azabutyronitrile derivatives, the modified Strecker method [4] was applied for the synthesis of the corresponding 2,2-tetramethylene analogs according to the lit. [5]. NMR spectra were determined with a Bruker AC 200 FT-NMR spectrometer and are expressed in ppm downfield from tetramethylsilane (internal standard).

4-Phenyl-3-aza-2,2-tetramethylene butyric acid derivatives **1e** and **1g**

To avoid hydrogen cyanide evolution a solution of potassium cyanide (30 mmol) in water (10 mL) was slowly added dropwise to a magnetically stirred mixture of benzylamine or N-methylbenzylamine (20 mmol), hydrochloric acid (20 mmol), 25% ethanol (40 mL) and cyclopentanone (20 mmol). The mixture was stirred 4 days and the resulting precipitate was filtered off (**1e**) or the reaction mixture was extracted with ether, dried with sodium sulfate and evaporated (**1g**). The nitriles were hydrolyzed to the corresponding acids with concentrated sulfuric acid at 20-100°C for 12 hours, followed by neu-

tralization and filtration or extraction, drying and evaporation. **1e**: 62%, m.p. 42-43°C; **1g**: 76%, b.p. 130-140°C / 0.45 Torr.

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Samples Availability: Not available.