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The preparation of the trihydrochloride form of 2-[3-(aminomethyl)-5-methyl-1,2,4-triazol-4-yl]-3-(2-chlorobenzoyl) thieno[2,3-*c*]-4,5,6,7-tetrahydropyridine (**2**) the ring opened derivative of a 1,2,4-triazolothieno-1,4-diazepine is described. Its structural properties are given, and are compared with those of the corresponding closed form 4*H*-6-(2-chlorophenyl)-1-methyl-7,8,9,10-tetrahydropyrido[4',3':4,5]thieno[3,2-*f*]-[1,2,4]triazolo[4,3-*a*][1,4]diazepine (**1**).

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### Introduction.

1,4-benzodiazepines are important minor tranquilizers. They have been extensively used as sedative, hypnotic, muscle relaxant, and anticonvulsant drugs [1]. Recently, benzo-1,4-diazepines and thieno-1,4-diazepines with a heterocyclic ring fused to the 1,2 position of the diazepine system have been shown to exhibit interesting pharmacological properties. They are imidazobenzodiazepines [2], triazolobenzodiazepines [3] and triazolothienodiazepines [4-6]. Some of the last ones are platelet-activity factor antagonists [7-9] and, for this reason, they have undoubtedly revived interest in this series.

It is well known that 1,4-benzodiazepines undergo acid-base hydrolysis in aqueous solution [10]. Owing to the pharmacological importance of these compounds, several studies of this reaction have been performed. They indicate that benzo-1,4-diazepines and thieno-1,4-diazepines with a heterocyclic ring fused to the 1,2 position hydrolyse on the 4,5-azomethine bond to give the corresponding benzo and thienophenones which reversibly cyclize into the original form in less acidic media [*inter alia* 1, 11-15]. Surprisingly, despite a very likely occurrence of "phenones" in physiological conditions, very few structural and physicochemical data concerning these ketones have been published. To our knowledge, only Konishi *and coworkers* [1] pointed out that they obtained the ketone of triazolam by synthesis without giving any more detail about its preparation nor its physicochemical characteristics. Jimenez *and coworkers* [16] have given some spectral data of this ketone, but the compound was not isolated. Analysis was performed in solution where the ketone stood in equilibrium with the parent diazepine. Finally, Gallo *and coworkers* [17] have also reported spectral data of the ketone derivatives from brotizolam, but the compound was only analysed in solution.

We report here the isolation of **2** in a satisfactory state of purity and describe some of its structural properties.

This work is connected with other studies concerning the parent benzodiazepine **1** and the compound **2**, as the

determination of the p*K*<sub>a</sub> values and the determination of kinetic constants [18-20]. The choice of **1** and **2** (see Figure 1) was dictated by our deliberate purpose to gain some insight into the thermodynamics and kinetics of "1,4-diazepines" in strictly aqueous solution. Sufficient aqueous solubility of these compounds was conferred by acidification of the tetrahydropyridino moiety to the *pH* values used for the thermodynamic and kinetic studies.

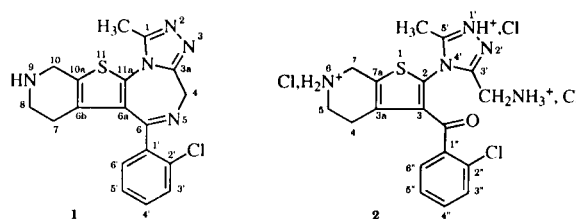


Figure 1: 4*H*-6-(2-chlorophenyl)-1-methyl-7,8,9,10-tetrahydropyrido[4',3':4,5]thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (**1**) and 2-[3-(aminomethyl)-5-methyl-1,2,4-triazol-4-yl]-3-(2-chlorobenzoyl)thieno[2,3-*c*]-4,5,6,7-tetrahydropyridine (**2**). (The numeration allows the attribution of the nmr signals).

### Results.

Compound **2** was prepared by treatment of compound **1** with concentrated hydrochloric acid as described in the experimental section. The obtained compound **2** was analyzed without further purification. Elemental analysis showed that **2** crystallised as a trihydrochloride with 2.4 molecules of water. Titration of chloride ions by the Mohr method gave exactly three equivalents. The titration of a sample in methanol, according to the Karl Fisher method, gave 8.8 p 100 of water which corresponded to 2.4 molecules by equivalent. The ir spectrum (4% in potassium bromide) exhibited, in addition to the NH<sup>+</sup> and NH<sub>2</sub><sup>+</sup> band at 3100-2400 cm<sup>-1</sup> and 3500-3300 cm<sup>-1</sup>, a characteristic band of carbonyl at 1664 cm<sup>-1</sup> (ν CO). There was no absorption at 1610 cm<sup>-1</sup>, which is characteristic of the imine bond (ν CN), which was present in the spectrum of **1**.

A comparison of the  $^1\text{H}$  nmr spectra of **1** and **2** showed different signals for the methylene protons of the aminomethyl group:

$$\begin{array}{l} \mathbf{2} \quad \delta = 3.88 \text{ ppm qd} \\ \mathbf{1} \quad \delta_{\text{B}} = 4.25 \quad \delta_{\text{A}} = 5.31 \quad \text{system AB} \quad J = 12.8 \text{ Hz} \end{array}$$

Moreover, an  $\text{NH}_3^+$  signal appeared at 8.97 ppm evidenced the fission of the benzodiazepine skeleton. An  $\text{NH}_2^+$  signal (tetrahydropyridino rest) at 10.12 ppm confirmed the isolation of the product under trihydrochloride salt (see Table 1). The methylene C7 of the tetrahydropyridino moiety and the methyl group presented two singlets. Signals of both methylene C4 and C5 looked like two enlarged singlets, the one of C4 presenting a shoulder. An irradiation at 3.3 ppm simplified the signal of the methylene C4, by causing the shoulder to disappear. The aromatic protons, in the correct integration ratios, were observed in the expected region.

Analysis of the  $^{13}\text{C}$  nmr data confirmed the presence of the carbonyl group ( $\delta_{\text{CO}} = 188.66$  ppm) as well as the change in the skeleton of the product. The signal of the methylene of the benzodiazepine ring at 33.37 ppm for **1** disappeared while a signal at 46.35 ppm appeared in the spectrum of **2**. All the other signals were distinguishable by comparison with  $^{13}\text{C}$  nmr data of **1** and **2** (compare with Table 2). The mass spectrum showed a quasimolecular ion  $(\text{M} + \text{H})^+$  at 388.0951 g when the theoretical mass was 388.0999 g.

Table 1

$^1\text{H}$  nmr data for **1** and **2** in DMSO- $d_6$ . Chemical Shifts are expressed in ppm [a]

1		2	
$\text{CH}_3$	2.59 ; s ; I = 3 H	$\text{CH}_3$	2.19 ; s ; I = 3 H
$\text{CH}_2$ (C7)	1.40 ; m ; I = 1 H 2.00 ; d ; I = 1 H	$\text{CH}_2$ (C4)	2.68 ; s ; I = 2 H
$\text{CH}_2$ (C8)	2.60 ; I = 1 H 2.80 ; m ; I = 1 H	$\text{CH}_2$ (C5)	3.30 ; s ; I = 2 H
$\text{CH}_2$ (C10)	$d_{\text{A}} = 3.89$ ppm $d_{\text{B}} = 3.85$ ppm $J^{\text{AB}} = 16.5$ Hz	$\text{CH}_2$ (C7)	4.43 ; s ; I = 2 H
$\text{CH}_2$ (C4)	$d_{\text{A}} = 5.31$ ppm $d_{\text{B}} = 4.24$ ppm $J^{\text{AB}} = 12.8$ Hz	$\text{CH}_2 \text{NH}_3^+$	3.88 ; qd ; I = 2 H
CH (C <sub>3',4',5',6'</sub> )	7.30-7.60 ; m ; I = 4 H	CH (C <sub>3'',4'',5'',6''</sub> )	7.40-7.56 ; m ; I = 4 H
NH (N <sub>9</sub> ) [b]	-	$\text{CH}_2 \text{NH}_3^+$	8.97 ; s ; I = 3 H
		$\text{NH}_2^+$ (N <sub>6</sub> )	10.12 ; s ; I = 2 H

[a] s: singlet, m: multiplet, d: doublet. [b] This signal does not appear.

It is worth noting that preliminary polarographic and uv spectrometric studies of **2** showed that it gives in acidic aqueous media the same states of equilibria as the corresponding thienodiazepine **1**. The isolation of **2** would be of great help for a thorough study of the equilibrium between

Table 2  
 $^{13}\text{C}$  nmr data of **1** and **2** in DMSO  $d_6$ .  
Chemical Shifts are expressed in ppm

Carbon	1	Carbon	2
$\text{CH}_3$	11.5	$\text{CH}_3$	10.01
C7	25.8	C4	21.73
C4	46.4	$\text{CH}_2\text{NH}_3^+$	33.4
C8	41.9	C5	40.2
C10	43.6	C7	41.2
C <sub>3'</sub> [a]	127.2	C <sub>3''</sub> [a]	127.9
C <sub>4'</sub> [a]	129.6	C <sub>4''</sub> [a]	129.5
C <sub>5'</sub> [a]	131.1	C <sub>5''</sub> [a]	130.0
C <sub>6'</sub> [a]	131.2	C <sub>6''</sub> [a]	133.7
C1'	131.4	C1''	129.8
C10a	132.4	C7a	130.2
C6b	130.9	C3a	131.5
C6a [b]	128.8	C3 [b]	133.1
C11a [b]	133.3	C2 [b]	136.4
C2'	137.7	C2''	136.4
C3a	159.0	C3'	149.6
C1	149.3	C5'	153.8
C6	164.3	C=O	188.7

[a] [b] undistinguishable carbons.

**1** and **2**. It would provide better knowledge of the behavior of 1,2,4-triazolothieno and probably of 1,2,4-triazolobenzo-1,4-benzodiazepines in water.

## EXPERIMENTAL

### Instrumentation.

The Melting point was determined on a Reichert apparatus and was uncorrected. The ir spectra were recorded in potassium bromide on a Perkin-Elmer IR-FT 16 PC between 400 and 4400  $\text{cm}^{-1}$ . The nmr spectra were run on a Bruker AM 300 WB apparatus. (Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes I, Campus de Beaulieu, 35042 Rennes Cédex, France). The pmr and cmr spectra were respectively recorded at 300.135 and 75.469 MHz in dimethylsulfoxide- $d_6$  solution with tetramethylsilane as the internal standard. The mass spectrum of **2** was run on a ZAB SpecTOF-VG Analytical in FAB conditions, with 3-nitrobenzyl alcohol as the matrix (Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes I, Campus de Beaulieu, 35042 Rennes Cédex, France).

### Reagents.

Compound **1** was kindly purchased for us by Ipsen-Beaufour Industry. The water used throughout this work was de-ionised on a set of ion exchanging columns (Bioblock Scientific, Illkirch, France) to  $\rho > 2 \text{ M}\Omega \cdot \text{cm}^{-1}$ . Hydrochloric acid 37% (Carlo Erba) and propan-2-ol (Prolabo) for organic synthesis were used.

2-[3-(aminomethyl)-5-methyl-1,2,4-triazol-4-yl]-3-(2-chlorobenzoyl)thieno[2,3-c]-4,5,6,7-tetrahydropyridine (**2**).

A solution of **1** (5g, 9,23 mmole) in 25 ml of water and 25 ml of concentrated hydrochloric acid was allowed to stand at room temperature overnight. 125 ml of propan-2-ol was added and the resulting mixture was then partially evaporated under reduce pressure (4 mm Hg) while keeping its temperature at room temperature.

As soon as the volume was reduced to the third of the initial one, 100 ml of propan-2-ol was added. The solution was then reduced again as described above. The precipitated crystals were collected by filtration and washed with propan-2-ol to yield **2** in quantitative amount and was analyzed without further purification, mp 258°; ir  $\text{cm}^{-1}$ , 1310-2400 and 3500-3300 ( $\text{NH}^+$  and  $\text{NH}_2^+$ ), 1610 (CO);  $^1\text{H}$  nmr (Table 1);  $^{13}\text{C}$  nmr (Table 2).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{18}\text{ClN}_5\text{OS} \cdot 3 \text{HCl} \cdot 2.4 \text{H}_2\text{O}$ : C, 39.85; H, 4.34; N, 12.92; O, 10.33; Cl, 26.20. Found: C, 40.13; H, 4.88; N, 13.01; O, 10.85; Cl, 25.52.

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