NMR Spectra and Conformational Analysis of Some 4,5-Dihydro-*s*-triazolo[3,4-*d*][1,5]benzothiazepine Derivatives

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High field ^1H and ^{13}C nmr spectra of a series of 1-substituted-4,5-dihydro-*s*-triazolo[3,4-*d*][1,5]benzothiazepine derivatives have been recorded. These have shown that, unless X = H or O, the molecules occur as a mixture of two slowly interconverting conformers at ambient temperatures. Variable temperature nmr experiments disclosed that the energy barrier to interconversion varies with the size of the substituent X located at position 1 of the fused *s*-triazole ring.

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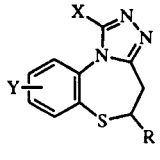
Introduction.

In continuation of our quest for novel pharmacologically active benzothiazepine derivatives, we have recently synthesized a series of substitued 4,5-dihydro-*s*-triazolo[3,4-*d*][1,5]benzothiazepines **1** and **2** [1-4]. Their structures have been verified by spectroscopic methods. Preliminary high field ^1H and ^{13}C nmr spectra disclosed that all derivatives with substituents other than R = H and X = H, O exhibited two sets of resonances suggesting the occurrence of these molecules in two solution forms. As no comprehensive nmr analysis of related benzothiazepines has been published in the literature, a detailed ^1H and ^{13}C nmr spectroscopic study of some representative members of these series has been undertaken and the results are reported in the sequel.



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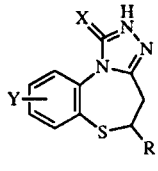

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Y = H, Cl
R = H, CH_3, C_6H_5
1 X = H, CH_3, C_6H_5, Br, CH_2Cl, CH_2NNCH_3, CH_2NO, $CH_2N(CH_3)_2$
2 X = O, S

The molecules studied were as follows. **1a**: R = Me, X = H, Y = Cl; **1b**: R = Me, X = Br, Y= Cl; **1c**: R = Me, X = Ph, Y = Cl; **1d**: R = Me, X = Me, Y = H; **1e**: R = Me, X = CH_2Cl, Y = H; **1f**: R = Me, X = $CH_2N(CH_3)_2$, Y= H; **2a**: R = Me, X = O, Y = H; **2b**: R = Me, X = S, Y = H.

Synthesis.

Preparation of **1a, 1c-f, 2a** and **2b** has been described elsewhere [1-4]. Derivative **1b** was obtained from **1a** by bromination in chloroform-pyridine (25:1) at refluxing temperature.

Results and Discussion.

NMR Analysis.

The fully assigned ^1H and ^{13}C spectral parameters are collected in Tables 1 and 2, respectively.

The most prominent fact about these data is that, with the exception of **1a** and **2a**, all derivatives exhibited two distinct sets of resonances for each observed (^1H and ^{13}C) sites suggesting the occurrence of two isomeric forms. Integration of the proton signals showed that the two forms are present in a 3:2 ratio and this value remains practically unchanged upon varying the X substituent from **1b** to **1f** or to **2b**. The nature of the resonance doubling became readily evident upon performing selective saturation experiments. Selective pre-irradiation of any resonance in the proton spectrum due to one of the two isomeric forms gave rise to saturation of the resonance due to the same proton site in the other isomeric form indicating that the two isomers are interrelated by slow (on the nmr time scale) interconversion process.

Inspection of the ^1H-^1H coupling constants (see Table 1) discloses that the two isomers differ primarily in the orientation of the Me group at C5 with respect to the methylene protons at C4. The values of the vicinal coupling constants $^3J_{4A,5}$ and $^3J_{4B,5}$ in the more abundant (major) isomer (11.4 and 6.5 Hz, respectively) are consistent with *antiperiplanar* relative orientation of C4-H_A and C5-H protons and *gauche* relative disposition of C4-H_B and C5-H. In the less abundant (minor) form these cou-

Table 1

1H NMR Spectral Data for Substituted 4,5-Dihydro-*s*-triazolo[3,4-*d*][1,5]benzothiazepines

	1a	1b		1c		1d		1e		1f		2a [a]	2b [b]	
		major component	minor component	major component	minor component	major component	minor component	major component	minor component	major component	minor component		major component	minor component
4-H_2	2.77	2.28	2.82	2.31	2.82	2.23	2.77	2.28	2 83	2.26	2.81	2.45	2.17	2.72
	3.30	3.56	3.24	3 57	3.28	3.48	3.16	3.54	3.22	3.50	3.18	2.97	3.27	2.93
5-H	3.93	3.74	4.04	3.80	4.08	3.71	4.01	3.73	4.04	3.72	4.01	3.70	3.58	3.91
5-CH_3	1.49	1.48	1.42	1.51	1.46	1.45	1.41	1.46	1.42	1.45	1.42	1.41	1.42	1.38
7-H	7.78	7.80	7.79	7.83	7.81	7.79	7.78	7.81	7.80	7.76	7.75	7.69	7.74	7.73
8-H	-	-	-	-	-	7.45	7.43	7.50	7.48	7.43	7.41	7.32	7.43	7.41
9-H	7.51	7.57	7.54	7.28	7.25	7.58	7.55	7.63	7.61	7.56	7.54	7.52	7.59	7.57
10-H	7.35	7.48	7.46	6.83	6.81	7.34	7.32	7.72	7.71	7.96	7.93	7.70	8.02	8.01
1-H	8.34	-	-	-	-	-	-	-	-	-	-	-	-	-
1-CH_3	-	-	-	-	-	2.49	2.50	-	-	-	-	-	-	-
1-CH_2	-	-	-	-	-	-	-	4.52	4.55	3.49	3.51	-	-	-
								4.91	4.93	3.56	3.57			
1-Ph	-	-	-	7.33-7.45	-	-	-	-	-	-	-	-	-	
$N(CH_3)_2$	-	-	-	-	-	-	-	-	-	2.27	2.27	-	-	-
exchangeable H	-	-	-	-	-	-	-	-	-	-	-	10.07	13.57	13.57
$^3J_{5,CH3}$	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.7	6.6	6.6
$^3J_{4A,5}$	7	11.3	6.9	11.5	6.3	11.4	6.5	11.3	6.6	11.4	6.5	6.9	11.2	6.6
$^3J_{4B,5}$	6	6.3	1.0	5.8	1.4	6.2	1.2	6.3	1.2	6.3	1.2	6.5	6.5	1.2
$^2J_{4A,4B}$	-14.5	-14.1	-14.3	-14.5	-14.5	-14.4	-14.4	-14.3	-14.3	-14.4	-14.4	-14.4	-14.4	-14.4
$^2J_{1-CH2}$	-	-	-	-	-	-	-	-12.6	-12.6	-13.4	-13.5	-	-	-

[a] Temperature: 60°C, [b] Solvent: deuteriochloroform + dimethyl sulfoxide-d_6.

Table 2

^{13}C Chemical Shifts (δ, ppm) for Substituted 4,5-Dihydro-*s*-triazolo[3,4-*d*]benzothiazepines

	1a	1b		1c		1d		1e		1f		2a[a]	2b[b]	
		major component	minor component	major component	minor component	major component	minor component	major component	minor component	major component	minor component		major component	minor component
C-1	142.1	135.4	135.3	153.2	153.4	150.3	150.5	150.1	150.2	151.3	151.5	154.0	166.6	166.7
C-3a	151.9	155.6	153.7	153.8	151.7	153.5	151.4	154.8	152.9	154.1	152.1	146.0	150.6	148.8
C-4	31.1	32.4	31.4	32.0	30.8	32.0	30.8	31.9	30.8	32.1	30.9	33.1	32.5	31.6
C-5	47.0	47.4	45.6	47.2	45.3	47.3	45.5	47.5	45.8	47.4	45.6	43.9	45.2	43.3
C-6a	129.2	128.9	131.7	128.5	131.3	127.0	129.9	127.0	129.9	126.4	129.4	126.8	125.7	128.8
C-7	136.3	137.0	136.0	136.8	135.7	137.6	136.4	137.8	136.6	137.3	136.0	136.4	137.1	135.8
C-8	134.7	127.5	127.7	126.2	126.3	129.2	129.2	129.9	129.9	129.0	129.0	128.4	129.3	129.3
C-9	130.4	130.3	130.2	130.1	129.9	130.2	130.1	130.7	130.6	130.2	130.0	130.4	129.8	129.7
C-10	124.6	127.1	127.1	127.2	127.4	124.9	125.0	124.8	124.8	125.9	126.0	125.6	127.6	127.7
C-10a	136.1	135.2	135.4	136.7	137.0	137.5	137.6	136.9	137.0	138.1	138.2	136.8	137.2	137.2
C5-*C*H_3	23.1	24.7	19.8	25.0	20.0	24.6	19.9	24.6	19.9	24.6	20.0	22.8	24.2	19.8
C1'		-	-	134.5	134.4	-	-	-	-	-	-	-	-	-
C2' + C6'		-	-	128.7	128.7	-	-	-	-	-	-	-	-	-
C3' + C5'		-	-	128.8	128.7	-	-	-	-	-	-	-	-	-
C4'		-	-	130.1	130.1	-	-	-	-	-	-	-	-	-
C1-*C*H_3		-	-	-	-	11.5	11.5	-	-	-	-	-	-	-
C1-*C*H_2		-	-	-	-	-	-	33.6	33.61	52.7	52.7	-	-	-
$N(CH_3)_2$		-	-	-	-	-	-	-	-	44.9	44.9	-	-	-

[a] Temperature: 50°C, [b] Solvent: deuteriochloroform + dimethyl sulfoxide-d_6.

plings assume substantially lower values (see Tables 1) reflecting a changed (*gauche-gauche*) steric disposition of pertinent protons.

In a recent nmr conformational analysis of substituted 1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones, Malik *et al.* [5] have measured the analogous vicinal coupling constants for the C4-Me derivatives and recorded the low temperature spectra where two different conformers could be identified. In each derivative studied by these authors, the low-temperature values of the coupling constants were

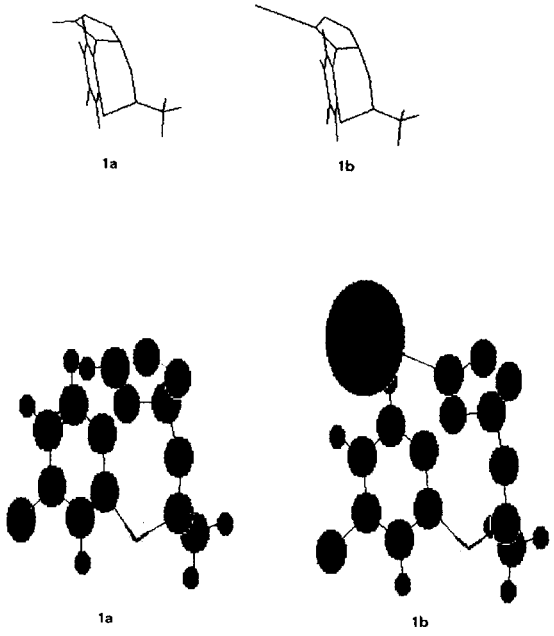

Figure 1. Perspective design showing the different steric interactions between the substituent at the 1-position and the bay region proton in 8-chloro-5-methyl-4,5-dihydro-1*H*-[1,2,4]triazolo[3,4-*d*][1,5]benzothiazepine **1a** and its 1-bromo derivative **1b**.

nearly identical with those observed in the present work and, also, the conformer with the antiperiplanar C3-H-C4-H arrangement was found to be the major constituent in each case. Accordingly, assuming a cycloheptadiene-like boat conformation for the seven-membered hetero ring, these authors concluded that the dominant conformer featured *quasi-axial* C4-Me group while the steric disposition of Me group in the minor conformer was *quasi-equatorial.*

Although the N(1)-C(2)O amidic bond in benzodiazepinones of ref [5] clearly implies a substantially lower torsional barrier to internal rotation of the seven-membered cycle than does the fused *s*-triazolo ring, it seems reasonable to assume that, by virtue of the close agreement between the relevant vicinal coupling costants, the two conformers observed in the present study possess about the same geometry as suggested by Malik *et al.*

As expected, interconversion between the two forms is also associated with characteristic changes in the chemical shifts of ^{1}H and ^{13}C resonances. Interpretation of these changes in terms of differences in geometry of the two conformers, however, is not straight-forward. While the conformation-induced chemical shift changes of the seven-membered ring protons can be readily attributed to the altered steric dispositions in the two forms, the actual ^{13}C shift values in the two conformers seem to depend on the molecular geometry in a more complex way. It may be noted that carbon atoms most affected by the change in conformation are the angular C6a ($\Delta\delta$: -2.7 - -2.8 ppm) and the C5-Me ($\Delta\delta$: +4.8-5.0 ppm).

The nearly equal occurrence of the two forms in solution (see above) indicates small (approximately 1 kJ.mol^{-1}) difference in the conformational energy of the conformers. In fact, inspection of Dreiding models shows that in none of these does a significant steric compression, originated by presence of the C2-Me group and its relative disposition, exist. This finding, like the observed vicinal couplings, are in complete agreement with observations made in ref [5].

The principal difference in the conformational behavior of the molecules reported here and in ref [5] is clearly the height of the energy barrier of the boat-boat ring inversion: it is high (two slowly interconverting forms at ambient temperature) for most of the derivatives studied here and low (one averaged form at room temperature) for molecules in ref [5].

The observation that derivatives **1a** and **2a** exhibit a single set of resonances in their ^{1}H and ^{13}C nmr spectra and the measured vicinal coupling constants of the seven-membered ring protons ($^{3}J_{4A,5} = 7$, $^{3}J_{4B,5} = 6$ Hz) reflect conformational averaging suggests that the major structural feature resulting in increased energy barrier cannot be associated with the mere presence of the fused *s*-triazole ring. Instead, our variable temperature ^{1}H nmr data (see Table 3) indicate that the principal contribution to the barrier height comes from the presence of the substituent at C1. In the transition state of the conformational inversion the bonds X-C1 and C10-H are nearly coplanar and, with X other than H or O, a severe steric interference between the substituent and C10-H occurs that causes an increase of about 30 to 40 kJ.mol^{-1} in the energy barrier. Supporting this view is the observation that the height of the energy barrier increases with steric demand of substituent X.

Table 3
Conformational Energy Difference (ΔG), C5-H Chemical Shift Difference ($\Delta\nu$), Coalescence Temperature (T_c) and Barrier Height (ΔE) for some Benzothiazepines in Dimethyl Sulfoxide-d_6 Solution [a]

X	ΔG	$\Delta\nu$	Tc	ΔE
Me	1	120	90	70
CH_2NMe_2	1	120	95	72
Ph	1	120	100	74
Br	1	120	125	80

[a] Energy values are in kJ.mol^{-1}, temperature in degrees C, chemical shift differences in Hz. ΔG values were estimated from signal intensities, ΔE values were calculated from the Eyring equation and the approximation $k_c = \pi\Delta\nu/(2)^{1/2}$, where k_c is the conformational exchange rate at the coalescence temperature.

EXPERIMENTAL

The melting point was determined using a Kofler hot-stage apparatus and is uncorrected. The mass spectrum was measured

with a LKB 2091 spectrophotometer at 70 ev. Elemental analysis was carried out on a Carlo Erba Analyzer model 1106. High field ^1H (400 MHz) and ^{13}C (100 MHz) nmr spectra for spectral assignments were run in deuteriochloroform solutions at ambient temperatures using Varian Associates model VXR-400 instrument with standard 1D and 2D experimental techniques. Assignments of quaternary carbon atoms were inferred from a series of site-selective (long-range) INEPT experiments [6]. Variable temperature measurements were performed in dimethyl sulfoxide-d_6 solutions.

Synthesis of 1-Bromo-8-chloro-4,5-dihydro-5-methyl-*s*-triazolo[3,4-*d*][1,5]benzothiazepine (**1b**).

A solution of bromine (2.9 g, 18 mmoles) in chloroform (15 ml) was added dropwise to a stirred solution of 1*H*-8-chloro-4,5-dihydro-5-methyl-*s*-triazolo[3,4-*d*][1,5]benzothiazepine (**1a**) (3.77 g, 15 mmoles) in chloroform:pyridine 25:1 (65 ml). The reaction mixture was stirred at room temperature for 10 minutes and then was refluxed for 7 hours. After cooling the solvent was evaporated under reduced pressure and the residue was taken up with chloroform, washed with 5% sodium thiosulphate solution and then with water. The chloroform phase was dried over sodium sulphate, filtered and brought to dryness *in vacuo*. The residue was purified by flash chromatography using chloroform as eluant to afford 3.32 g (67%) of 1-bromo-8-chloro-4,5-dihydro-*s*-triazolo[3,4-*d*][1,5]benzothiazepine, mp 145-147°; ms: (70 eV, electron impact) m/z 331 (M^+).

Anal. Calcd. for $C_{11}H_9BrClN_3S$: C, 39.96; H, 2.74; N, 12.74. Found: C, 40.18; H, 2.73; N, 12.40.

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