1,3-THIAZEPINES. 5*. STUDY OF 2-PHENYL(BENZYL)-IMINOHEXAHYDRO-1,3-THIAZEPINES AND THEIR DERIVATIVES BY ^{13}C SPECTROSCOPY

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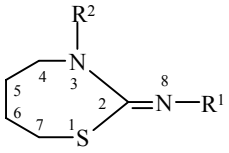
We have studied the ^{13}C NMR spectra of 2-phenyl- and 2-benzyliminohexahydro-1,3-thiazepines, and also their alkyl, acyl, carbamoyl, and thiocarbamoyl derivatives. We have shown that introducing substiuents both into the 2 position and into the 3 position of the thiazepine ring mainly affects the chemical shifts for the C(4) of the heterocycle.

Keywords: aminotetrahydro-1,3-thiazepines, 2-phenyl(benzyl)iminohexahydro-1,3-thiazepines.

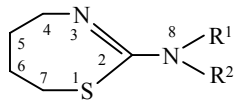
In a continuation of the study of the chemical and physicochemical properties of aminotetrahydro- and iminohexahydrothiazepines [1, 2], we have studied the ^{13}C NMR spectra of this series of compounds. The ^{13}C NMR spectra of amino(imino)thiazepines and their hydrogenated analogs are described in the literature for 2-(2',6'-dichlorophenyl)iminohexahydro-1,3-thiazepine and its methylated derivative [3]. It is precisely on the basis of the ^{13}C NMR spectra that both compounds are assigned the structure of imines.

Generalized data on the spectral properties of heterocyclic analogs of thiourea, including hydrogenated derivatives of thiazepine, have made it possible to conclude that in distinguishing between tautomeric amino and imino structures, reliable results are provided only by ^{13}C NMR spectroscopy supplemented with X-ray diffraction data [4].

As the objects of investigation, we selected the following iminohexahydrothiazepines **1-4** and aminotetrahydrothiazepines **5-12**:



1–4



5–12

1, **3-6**, **8**, **10**, **11** R^1= Ph; **2**, **7**, **9**, **12** R^1= CH_2Ph; **1**, **2** R^2= H, **3** R^2= Me, **4** R^2= CH_2CH_2COOMe, **5**, **7** R^2= COMe, **6** R^2= COPh, **8**, **9** R^2= CONHPh, **10** R^2= CSNHMe, **11**, **12** R^2= $CSNHCH_2Ph$

* For Communication 4, see [1].

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We described the synthesis of all the compounds, except compounds **3** and **7**, earlier in [1, 2, 5, 6]. Compound **3** was obtained by methylation of imine **1** with methyl iodide. Compound **7** was synthesized by acetylation of imine **2** with acetyl chloride.

The signals in the ^{13}C NMR spectra were assigned based on additional polarization transfer experiments (DEPT experiments) and heterocorrelation by the direct and long-range constants (respectively HMQC and HMBC experiments). We should note that detection of C(2) signals was often difficult. The same was noted earlier in [7], when it was not always possible to assign δ C(2) in ^{13}C NMR spectra of benzothiazepines.

Analysis of the chemical shifts (Table 1) reveals that only the signal of the C(4) atom appreciably responds to the nature of the substitution. But the position of even this signal cannot be used as a criterion for the nature of the substitution: the range of variation in the chemical shifts of C(4) in the studied compounds is practically the same for both imino and amino derivatives (within the range 45-53 ppm).

The position of this signal (se Fig. 1), allows to pick out two characteristic clusters for both the iminohexahydrothiazepines (clusters **A** and **B**) and aminotetrahydrothiazepines (clusters **C** and **D**). Among imines **1-4**, the signal for the C(4) atom is shifted downfield by ~6 ppm (cluster **A**) only in the spectrum of compound **1**, the simplest of the compounds under consideration. For this case, we probably observe the most favorable conditions for overlapping of the lone electron pairs of the two nitrogen atoms, the sulfur, and the π-electrons of the C(2)–N(8) double bond with the π-electrons of the benzene ring. In all the rest of the compounds, the π-electron system of the heteroatoms of the ring is somewhat distorted by additional substituents or disrupted by a phenyl→benzyl change in one of the substituents. Cluster **B** exhibits passivity of the C(4) signal both to alkyl substitution at N(3) and to the nature of the substitution (phenyl/benzyl) at N(8).

Amines **5-12** are assigned to two characteristic clusters according to the value of the chemical shift: **C** includes compounds with a carbonyl functional group in the substituent, **D** includes compounds with a thiocarbonyl group, which probably also is due to the nature of the overlap of the lone electron pairs of the oxygen or sulfur atoms with the π-electron system of the heteroatoms of the tetrahydrothiazepine ring. All the remaining changes in the substituents have practically no effect on the position of the C(4) signal (Table 1).

Comparison of the position of the clusters on a chemical shift scale shows that the spread within a group (amines or amines) is greater than the spread between groups.

The C(2) signal is shifted downfield by ~4 ppm practically only in the spectrum of compound **2**. This may be explained by the only case (among the considered compounds) of disruption of the conjugation of the electron system of the hexahydrothiazepine ring with any π-electron system of the substituents. In the spectra of all the remaining compounds, the C(2) signal is quite independent of the nature of the substitution.

The values of the chemical shifts for C(4') (Table 1), from the authors of [3], also cannot serve as a criterion for distinguishing amino and imino structures. In the spectra of iminohexahydrothiazepines (**1, 3, 4**), this signal appears at 123.5±1.1 ppm, while for amino derivatives (**5, 6, 8, 10, 11**) it appears at 124.7±0.1 ppm. Considering that the imino derivatives have alkyl substituents in the N(3) position while the amino derivatives have substituents only with π-electron systems, it is not entirely proper to compare the indicated chemical shifts. Such similar values for them raises doubts concerning the very use of the C(4') signal for establishing the type of substitution of the hydrogenated thiazepine.

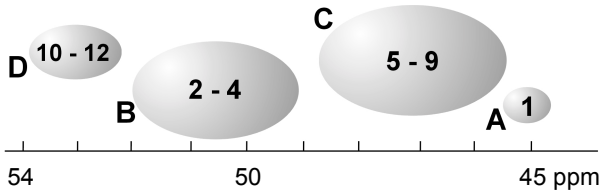

Fig. 1. Position of the C(4) signal in compounds **1-12**.

TABLE. ^{13}C NMR Spectra of Compounds **1-12**, δ, ppm

Com-pound	Heterocycle					R^1					R^2					
	C(2)	C(4)	C(5)	C(6)	C(7)	C(1')	C(2')	C(3')	C(4')	CH_2	C(1")	C(2")	C(3")	C(4")	CO, CS	CH_3, [CH_2]
1	160.45	45.04	29.95	30.33	32.04	149.17	122.05	128.55	122.58							
2	155.68	49.85	28.72	30.36	31.34	139.23	127.91	128.58	127.21	48.33						
3	158.36	51.02	27.86	29.66	31.75	148.27	126.84	129.00	125.64							41.23
4	156.89	51.49	28.34	29.37	32.56	151.08	122.18	128.33	122.22						172.73	51.49*
5	159.64	46.17	26.88	30.18	31.67	148.23	119.65	129.19	124.78						169.12	23.28
6	159.17	46.21	27.72	30.02	32.10	148.02	119.24	128.82	124.45		136.57	127.53	128.22	130.37	169.78	
7	157.84	46.16	26.82	30.62	31.37	138.63	128.03	128.63	127.13	56.47					170.30	22.86
8	160.54	48.25	29.08	28.52	33.48	147.81	121.28	129.07	124.67		138.46	119.85	128.97	123.46	152.76	
9	159.00	47.40	28.40	29.00	32.60	138.80	127.70	128.60	127.00	56.60	139.50	119.30	128.60	122.70	152.80	
10	160.89	53.62	28.32	29.19	33.19	147.47	120.98	129.12	124.83						183.96	32.72
11	160.62	53.52	28.14	29.24	33.10	147.09	120.84	128.97	124.87		137.23	127.81	128.77	127.63	182.50	[50.46]
12	159.45	52.97	27.95	29.35	32.38	138.56	127.48	128.47	127.32	56.33	137.12	127.81	128.54	126.92	182.30	[50.06]

* δ, ppm: 47.52 (α-CH_2); 32.41 (β-CH_2).

Thus from the analysis results we must conclude that the π-electron system of the double bond and the lone electron pairs of the three heteroatoms in hydrogenated derivatives of amino(imino)-1,3-thiazepine have a rather complex conjugation system, and do not respond so simply to the presence of substituents in the N(3) and N(8) positions as might be expected from the structural formula. A more reliable assignment of the other compounds to amino or imino derivatives probably may be made only by using X-ray diffraction results.

EXPERIMENTAL

The ^{13}C NMR spectra in $CDCl_3$ were recorded on a UNITY plus 400 spectrometer with operating frequency 100 MHz, internal standard TMS; the ^1H NMR spectra were recorded on a Tesla BS-567 (100 MHz), internal standard HMDS. The IR spectra were taken on a UR-20 in KBr disks. The purity of the synthesized compounds were monitored by TLC (Silufol UV-254).

3-Methyl-2-phenyliminohexahydro-1,3-thiazepine (3). CH_3I (3 g, 22 mmol) was added to a suspension of thiazepine **1** (2.06 g, 10 mmol) in absolute ethanol (10 ml) and refluxed for 10 h. The reaction mixture was evaporated down under vacuum to dryness; the residue was dissolved in water and neutralized with base. The precipitated oil was extracted with ether (3×20 ml). The ether extract was dried with $CaCl_2$ and saturated with HCl. The precipitate was filtered out, recrystallized from water, and then dissolved in hot water and neutralized with sodium carbonate. The oil obtained was washed with water and dried. Yield of compound **3** 1.8 g (82%), R_f 0.57 (benzene–acetone, 1:3). IR spectrum, ν, cm^{-1}: 1620 (C=N). ^1H NMR spectrum, δ, ppm: 1.48-2.05 (4H, m, $C(CH_2)_2C$); 2.54 (2H, t, CH_2S); 3.18 (3H, s, CH_3); 3.67 (2H, t, CH_2N); 6.98-7.40 (5H, m, C_6H_5). Found, %: C 65.20; H 7.36; N 12.58. $C_{12}H_{16}N_2S$. Calculated, %: C 65.41; H 7.32; N 12.71.

2-(N-Acetyl-N-benzylamino)tetrahydro-1,3-thiazepine (7). Triethylamine (1.1 g, 10 mmol) along with a solution of CH_3COCl (0.8 g, 10 mmol) in absolute acetone (3 ml) (dropwise at a temperaturee no higher than 10°C) were added to a solution of thiazepine **2** (2.2 g, 10 mmol) in absolute acetone (10 ml), The mixture was allowed to stand for 10 h with periodic shaking at room temperature, then was refluxed for 0.5 h and evaporated down. The remaining oil was washed with dilute HCl, then with water, and was purified on a column with silica gel L 100/160, eluting first with hexane and then with chloroform. Obtained 1.78 g (68.5%) of compound **7**; mp 57-58°C (hexane), R_f 0.64 (benzene–chloroform–acetone, 1:1:1). IR spectrum, ν, cm^{-1}: 1680 (C=O), 1620 (C=N). ^1H NMR spectrum, δ, ppm: 1.50-2.09 (4H, m, $C(CH_2)_2C$); 2.03 (3H, s, CH_3); 2.85 (2H, t, CH_2S); 3.62 (2H, t, CH_2N); 4.42 (2H, s, CH_2Ph); 7.15-7.52 (5H, m, C_6H_5). Found, %: C 63.95; H 6.98; N 10.52. $C_{14}H_{18}N_2OS$. Calculated, %: C 64.09; H 6.91; N 10.68.

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