STUDY OF CHLORO DERIVATIVES OF PYRIDAZINE AND THE PRODUCTS OF SILYLATION OF PYRIDAZINE AND 6-PYRIDAZONE DERIVATIVES BY Cl^{35} NUCLEAR QUADRUPOLE RESONANCE

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The structures of a number of chloro derivatives of pyridazine and products of trimethylsilylation of chloro derivatives of pyridazine and 6-pyridazone were confirmed on the basis of data from their Cl^{35} nuclear quadrupole resonance spectra, and the effect of substituents in the 6 position of the pyridazine ring on the chlorine atom in the 3 position was investigated.

Organosilicon derivatives of nitrogen-containing heterocyclic compounds are currently widely used for the synthesis of nucleosides. We have suggested that trimethylsilyl derivatives of pyridazines, obtained by treatment of the corresponding pyridazine and 6-pyridazine derivatives with hexamethyldisilazane in the presence of a small amount of trimethylchlorosilane, be used for the preparation of pyridazine analogs of nucleosides [1]. In this case the reaction products may be trimethylsilyl derivatives of pyridazine or 6-pyridazone.

One can make a choice between the possible structures of the products of trimethylsilylation on the basis of data from the nuclear quadrupole resonance (NQR) spectra by comparing them with the spectra of similarly constructed model compounds. The latter were chloro derivatives of 6-pyridazone [2] and pyridazine (Table 1), the Cl^{35} NQR spectra of which have not been investigated up to now (except for 3,6-dichloro- and 3,4,5,6-tetrachloropyridazine [3]).

The NQR frequencies of 3-chloro-6-substituted pyridazines (Table 1) are considerably higher than the frequencies of the corresponding chlorobenzene derivatives; this is due to the presence in the pyridazine ring of two electronegative nitrogen atoms. The Cl^{35} NQR frequency of p-substituted chlorobenzene decreases in conformity with the Hammett substituent (R) constants on passing from R = Cl to R = OCH_3 and NH_2. The ν^{77} values of 3-chloro-6-substituted pyridazines also decrease on passing from R = Cl to R = OCH_3. When R = NH_2, the NQR frequency is somewhat higher than when R = OCH_3; this is not in conformity with the δ constants of these substituents. This anomaly may be due to a crystal effect.

Inasmuch as each chlorine atom in the 3,6-dichloropyridazine and 4,6-dichloropyrimidine molecules is in the α position relative to the endocyclic nitrogen atom, one might have expected that the NQR frequencies of these compounds would prove to be close. However, the NQR spectrum of 3,6-dichloropyridazine is found in a considerably higher-frequency region than that of 4,6-dichloropyrimidine. If the nitrogen atoms in these compounds affect their NQR frequencies in the same way as in chloro derivatives of pyridine (i.e., the nitrogen atom in the β position relative to the chlorine atom has the strongest electron-acceptor effect on the chlorine atom, the electron-acceptor effect of the γ-nitrogen atom is somewhat weaker, and the α-nitrogen atom displays electron-donor properties [4-7]), the nitrogen atoms in the α positions relative to the chlorine atoms of 3,6-dichloropyridazine and 4,6-dichloropyrimidine should lower their NQR frequencies. The nitrogen atoms of

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TABLE 1. Cl^{35} NQR Frequencies at 77° K (ν^{77}) of Chlorine-Containing Pyridazine Derivatives

No.	R^3	R^4	R^5	R^6	ν^{77}, MHz	Relative intensity of the signals
1	Cl	H	H	Cl	36,403	2
					36,013	1
					35,902	1
2	Cl	H	H	OCH_3	35,256	2
					35,236	2,5
					35,062	1
3	Cl	H	H	NH_2	35,266	
4	Cl	H	H	$OSi(CH_3)_3$	35,351	
5	Cl	H	H	$NHSi(CH_3)_3$	35,250	1
					35,089	3
					34,829	2
6	Cl	Cl	Cl	H	38,315	1
					38,226	1,5
					37,863	8,5
					37,627	4
					37,123	3
					36,997	2,5
					36,749	7
7	H	Cl	Cl	$OSi(CH_3)_3$	37,972	
					37,881	
					36,804	
					36,419	
8	$OSi(CH_3)_3$	Cl	Cl	$OSi(CH_3)_3$	37,657	1
					37,623	1
9	H	$NHSi(CH_3)_3$	Cl	$OSi(CH_3)_3$	35,950	
10	H	$NSi(CH_3)_3(COCH_3)$	Cl	$OSi(CH_3)_3$	37,215	

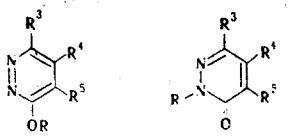
3,6-dichloropyridazine in the α position relative to the chlorine atoms should increase their NQR frequencies to a greater extent than the nitrogen atoms in the γ position relative to the chlorine atoms in 4,6-dichloropyrimidine.

The chlorine atoms in the 4,6-dichloropyrimidine molecule are closer to one another than in the 3,6-dichloropyridazine molecule. The drawing together of the chlorine atoms leads to an increase in their NQR frequencies, as is observed, for example, in the case of dichlorobenzenes [8]. The difference between the electron-acceptor effect on the chlorine atoms in these two compounds of the nitrogen atoms in the β and γ positions with respect to the chlorine atoms evidently exceeds the difference between the effect of the chlorine atoms bonded to the β and γ-carbon atoms of the corresponding heterocycle, and this is also responsible for the increase in the NQR frequency of 3,6-dichloropyridazine as compared with 4,6-dichloropyrimidine. Of course, this conclusion is valid only if the effects on the chlorine atoms of the nitrogen atoms in the α position relative to them are practically identical in both molecules.

The Cl^{35} NQR spectrum of 3,4,5-trichloropyridazine is also found in a higher-frequency region than that of 4,5,6-trichloropyrimidine. The low-frequency lines in the NQR spectra of these compounds belong to the chlorine atoms in the α position relative to the nitrogen atoms of the corresponding ring, and the NQR frequency of the low-frequency line in the spectrum of 3,4,5-trichloropyridazine is appreciably higher than the two low-frequency lines in the spectrum of 4,5,6-trichloropyrimidine (ν^{77}=35.850 and 36.060 MHz [9]). This can be explained in the same way as in the preceding case. The high-frequency portion of the spectrum, the assignment of the lines in which is impossible, belongs to the chlorine atoms in the 4 and 5 positions in 3,4,5-trichloropyridazine. Their NQR frequencies are close to the Cl^{35} NQR frequency of the chlorine atom in the 5 position in 4,5,6-trichloropyrimidine (ν^{77}=37.996 MHz [9]).

As in the case of other organic chloro derivatives, the NQR frequency of a given chlorine atom in the NQR spectra of chloro-substituted pyridazines increases as the number of chlorine atoms in the molecule increases (see, for example, the Cl^{35} NQR spectra of 3,6-dichloro- and 3,4,5-trichloropyridazines, which are presented in Table 1, and the spectrum of 3,4,5,6-tetrachloropyridazine) [3].

The Cl^{35} NQR frequencies of the corresponding chloro derivatives of pyridazine (Table 1) and 6-pyridazone [2] differ substantially. Thus, for example, the NQR frequency of 3-chloro-6-pyridazone (ν^{77}=36.523 MHz [2]) is ~1.0 MHz higher than the NQR frequency of 6-methoxy- and 6-amino-3-chloropyridazine and 0.33 MHz higher than the frequencies of 3,6-dichloropyridazine. This provides a possibility, by comparing the NQR spectra of chloro derivatives of 6-pyridazone and pyridazine with their corresponding trimethylsilylation products, to determine the structure of the latter.



I II

The formation of a compound corresponding to structure I or II is possible in the silylation of 3-chloro-6-pyridazone. On the basis of the Cl^{35} NQR spectra of 3-chloro-6-substituted pyridazines and 3-chloro-6-pyridazones it may be assumed that the NQR frequency of 3-chloro-6-trimethylsiloxypyridazine (I) should be close to 35 MHz and that of 1-trimethylsilyl-3-chloro-6-pyridazone (II) should be close to 36 MHz. The NQR spectrum of the product of silylation of 3-chloro-6-pyridazone (ν^{77}=35.351 MHz) consequently corresponds to structure I.

The Cl^{35} NQR spectrum of the product of silylation of 3-chloro-6-aminopyridazine, which is found at ~35 MHz, indicates that this compound is 3-chloro-6-trimethylsilylaminopyridazine (I).

If 1-trimethylsilyl-4,5-dichloro-6-pyridazone [structure II, R = Si$(CH_3)_3$, R^3=H, R^4=R^5=Cl] had been formed in the silylation of 4,5-dichloro-6-pyridazone, the NQR frequencies of the starting compound and the reaction product would differ only slightly, inasmuch as the changes in the structures of the starting molecule as a result of the reaction would have occurred relatively far away from the indicator chlorine atoms. In actuality, however, the electron density distributions on the chlorine atoms of 4,5-dichloro-6-pyridazone and the reaction product differ substantially. The NQR spectrum of 4,5-dichloro-6-pyridazone consists of two closely situated lines (ν^{77}=37.435 and 37.220 MHz [2]), whereas the two low-frequency lines in the quadruplet spectrum of the reaction product differ substantially from the two high-frequency lines with respect to their frequencies. The low-frequency pair of lines in this spectrum is considerably lower in frequency, whereas the high-frequency pair of lines is considerably higher in frequency than the lines in the spectrum of 4,5-dichloro-6-pyridazone. A comparison of the spectra of the starting compound and the reaction product provides evidence that the product of silylation of 4,5-dichloro-6-pyridazone is evidently 4,5-dichloro-6-trimethylsiloxypyridazine (I).

If it is assumed that as the chlorine atom becomes farther away from the $(CH_3)_3SiO$ grouping in the chloro derivative of 6-trimethylsiloxypyridazine its NQR frequency changes in the same way as the spectra of compounds of the $(CH_3)_3SiO(CH_2)_nCl$ series,* the high-frequency doublet in the NQR spectrum of 4,5-dichloro-6-trimethylsiloxypyridazine should be assigned to the chlorine atom in the 5 position, and the low-frequency doublet should be assigned to the chlorine atom in the 4 position.

The formation of O,O-, N,N-, or O,N-trimethylsilyl derivatives is possible in the silylation of 3-hydroxy-4,5-dichloro-6-pyridazone. The NQR spectrum of the silylation product consists of two very close frequencies ($\Delta\nu$ = 0.034 MHz) and lines of identical intensities. This indicates practically complete equivalence of the chlorine atoms in the molecule and the relatively high symmetry of the molecule. Consequently, the silylation product is the O,O- or N,N-trimethylsilyl derivative. It is impossible to make a choice between these two structures on the basis of the currently available data from the Cl^{35} NQR spectra.

The lack of the corresponding model compounds made it impossible to confirm the structures of compounds 9 and 10 in Table 1, which were established on the basis of their UV, IR, and PMR spectra [1].

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*Data from the present research (ν^{77}=32.379, 33.655, and 32.734 MHz when n=1, 2, and 3, respectively). The compounds of this series were synthesized by I. Pola and V. Khvalovskii, to whom the authors express their gratitude.

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MASS-SPECTROMETRIC STUDY OF 2- AND 4-THIOBARBITURIC ACID DERIVATIVES

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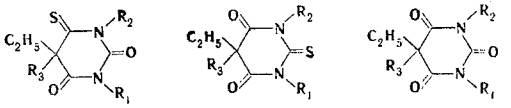
The mass spectra of 2- and 4-thiobarbituric acids and some of their close analogs at ionizing voltages of 70 and 14 eV are compared. Qualitative and quantitative differences in the behavior of these compounds under the influence of electron impact were established. It is shown that the position of the thione group in the ring and the tautomeric transformations have a substantial effect on the character of the fragmentation of the investigated compounds. The established fragmentation principles make it possible to distinguish the structural isomers in a series of 2- and 4-thiobarbituric acids from their mass spectra.

The mass spectra of barbituric acid derivatives have been studied by many investigators [1-7]. However, the peculiarities of the behavior of compounds of this class under the influence of electron impact have not been completely evaluated, inasmuch as the high-resolution spectra, the spectra at low ionizing-electron energies, and model analogs with isotopic and chemical labels have not been studied systematically in the early papers [1-3] and the later papers [6, 7].

In the present paper we present a comparison of the mass spectra of 2- and 4-thiobarbituric acids (I-X) and their close analogs (XI, XII) with the application of deuterium labeling, metastable ions, and data from high-resolution mass spectrometry and mass spectrometry with low-energy electrons. The mass spectra of 4-thiobarbituric acid derivatives I-VII were obtained for the first time. It should be noted that the spectra of VIII and X-XII also have practically not been discussed previously [1].



I-VII VIII-X XI-XII

I $R_1=R_2=H$; $R_3=C_2H_5$; II $R_1=R_2=D$; $R_3=C_2H_5$; III $R_1=R_2=H$; $R_3=C_3H_7$; IV $R_1=R_2=H$; $R_3=\frac{C_3H_7}{H_3C}\!\!>\!\!CH$; V $R_1=H$; $R_2=CH_3$; $R_3=C_2H_5$; VI $R_1=CH_3$; $R_2=H$; $R_3=C_2H_5$; VII $R_1=R_2=H$; $R_3=C_6H_5$; VIII $R_1=R_2=H$; $R_3=C_2H_5$; IX $R_1=R_2=D$; $R_3=C_2H_5$; X $R_1=R_2=H$; $R_3=\frac{C_3H_7}{H_3C}\!\!>\!\!CH$; XI $R_1=R_2=H$; $R_3=C_6H_5$; XII $R_1=C_6H_5$—CO; $R_2=H$; $R_3=C_6H_5$

The behavior under electron impact of structural isomers I, VIII and IV, X can be compared with respect to the W_M* values and the relative intensities of the peaks of the characteristic fragments. The differences in the fragmentation under electron impact of I, VIII and IV, X are manifested primarily in the W_M values. We found that the W_M value for I is 5 at 70 eV and increases to 35 as the ionizing voltage is lowered to 14 eV. In the case of VIII this parameter under the same conditions is characterized by higher values of, respectively,

* The W_M value is the relative stability of the molecule with respect to electron impact and is equal to $I[M+\cdot]/\Sigma I$; $[M+\cdot]$ is the intensity of the molecular ion peak, and ΣI is the total ion current.

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