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NMR SPECTRA OF CYCLIC NITRONES.

5*. ^{13}C NMR SPECTRA OF THE POTENTIAL TAUTOMERIC SYSTEMS OF AMINO-, HYDROXY-, AND MERCAPTONITRONES IN THE SERIES OF 3-IMIDAZOLINE 3-OXIDE

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UDC 543.422+547.781.3

The position of the tautomeric equilibrium in amino-, hydroxy, and mercaptonitrones was determined by the ^{13}C NMR method for the case of the derivatives of 3-imidazoline-3-oxide. It was shown that the tautomeric equilibrium in the OH and SH derivatives is shifted toward the oxo and thioxo forms (∿95%). The chemical shifts of the carbon atoms of the nitrone group in the α-N-, α-O-, and α-S-substituted nitrones lie in the region of 137-150 ppm.

While continuing a systematic study of the properties of cyclic nitrones, we investigated the ^{13}C NMR spectra of 3-imidazoline-3-oxides, containing N-, O-, and S-substituents at the α-carbon atom, and we also used this method to investigate the possibility of tautomerism of the keto–enol type in hydroxy- and mercaptonitrones. The available published data do not make it possible to reach a conclusion about the realization of such tautomerism [2].

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The question of the preferred existence of the amino derivatives in the form of the aminonitrone (AN) in the 2-aminopyrroline 1-oxide series was resolved on the basis of an analysis of their IR spectra [3]. The most suitable method for investigation of the tautomerism of the amino, hydroxy, and mercapto derivatives of pyridine proved to be the ^{14}N NMR method, whereas the ^{13}C NMR method only made it possible to estimate the position of the tautomeric equilibrium qualitatively as a result of the small differences in the chemical shifts [4, 5]. On the other hand, for these reasons neither method made it possible to determine quantitatively the position of the tautomeric equilibrium in the corresponding derivatives of pyridine N-oxide [6].

*For Communication 4, see [1].

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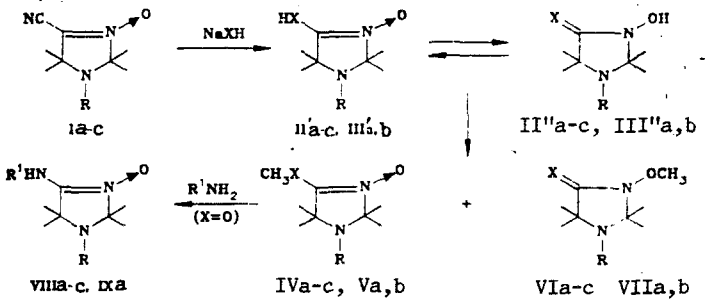
TABLE 1. The Data from the ^{13}C NMR Spectra of Compounds (II-IX)

Compound	Solvent	Chemical shifts, ppm					
		$C_{(4)}$	$C_{(2)}$	$C_{(5)}$	2,5-CH_3	N—CH_3	X—CH_3
Hydroxy-oxo derivatives							
IIa	DMSO	169,0	76,8	58,4	23,4; 23,0	26,7	—
	CCl_4	169,5	78,1	59,3	23,5; 22,9	26,8	—
	CH_3OH	170,7	79,3	60,8	22,9; 22,5	27,0	—
IIb	DMSO	165,2; 164,9	79,9; 70,4	62,0; 62,3	27,1; 21,5; 26,6; 22,3	—	—
IVa	DMSO	150,9	85,9	59,8	23,4; 22,8	26,7	58,2
	CCl_4	152,5	86,6	60,5	23,6; 23,0	26,5	60,5
	CH_3OH	156,7	87,5	61,6	23,4; 22,6	26,3	60,1
IVb	DMSO	147,1; 147,0	87,7; 86,8	63,5; 64,1	26,4; 21,3; 23,4; 22,8	—	59,6
VIa	DMSO	170,1	77,1	58,2	23,4; 22,8	26,3	64,2
	CCl_4	168,7	77,3	59,0	23,5; 23,1	26,9	64,2
	CH_3OH	171,1	78,8	59,9	23,1; 22,7	26,9	64,7
VIb	DMSO	166,1	80,3; 79,6	62,2; 62,6	27,3; 21,3; 26,4; 22,6	—	65,2
Mercapto-thioxo derivatives							
IIIa	DMSO	189,8	82,8	67,6	24,8; 22,6	26,7	—
	CCl_4	184,5	83,5	68,5	25,3; 23,6	27,0	—
	CH_3OH	190,8	84,8	69,5	23,5; 23,1	27,2	—
IIIb	DMSO	188,7; 187,7	85,6; 85,3	72,2; 72,7	30,0; 22,3; 27,4; 24,3	—	—
	CH_3OH	189,4; 188,3	86,7; 85,6	72,6; 73,4	29,5; 21,8; 26,9; 24,1	—	—
Va	DMSO	138,1	89,6	64,5	23,7	27,1	11,2
	CCl_4	139,2	90,1	64,7	24,1	27,4	11,7
	CH_3OH	147,8	91,1	66,3	23,7	26,9	12,1
Vb	DMSO	137,9; 137,8	90,6; 89,9	68,1; 68,6	27,7; 22,2; 27,4; 22,2	—	11,8
	CH_3OH	144,0; 143,2	92,2; 91,3	69,5; 70,3	27,8; 22,2; 27,4; 22,5	—	—
VIIa	DMSO	192,5	84,0	68,7	25,6; 23,5	27,2	63,0
	CCl_4	195,3	83,8	69,2	25,9; 23,7	27,4	63,0
	CH_3OH	196,3	85,0	69,7	25,6; 23,4	27,1	63,3
VIIb	DMSO	191,6; 190,1	86,2; 85,2	72,2; 72,6	29,7; 22,3; 27,9; 24,1	—	64,3
	CH_3OH	193,7; 191,8	86,9; 85,7	72,9; 73,6	29,8; 22,2; 27,2; 24,3	—	64,3 64,0
Amino derivatives							
VIIIa	$CDCl_3$	149,4	84,5	60,6	23,5	26,6	—
	CH_3OH	153,3	84,8	61,3	23,0; 22,9	25,8	—
VIIIb	CH_3OH	150,8; 150,2	86,9; 86,0	64,8; 65,9	26,9; 21,9	—	—
IXa	$CDCl_3$	148,4	83,4	60,5	23,4; 23,0	25,9	28,7

In the present work we studied the 1-methyl (a) and 1-nitroso (b) derivatives of 3-imidazoline 3-oxide, which differ in the electronic effect of the substituent at the $N_{(1)}$ atom [7-9], and this could affect the position of the tautomeric equilibrium [10].

The investigated hydroxy (II) and mercapto (III) derivatives were obtained by the reaction of the nitriles (I) with sodium hydroxide [11] and sodium sulfide [12], while the corresponding model compounds were obtained by the alkylation of (II) and (III). Thus, alkylation of the hydroxy derivatives (IIa, b) by diazomethane and ether gives the methoxynitrones (IVa, b) and the hydroxamic esters (Va, b) in similar amount (~ 30 and 40%), whereas the reaction with methyl iodide in alcohol solution in the presence of alkali only gives the hydroxamic esters (VIa, b). A different pattern is observed during the alkylation of the mercapto derivatives (IIIa, b). In the reaction of (IIIa, b) with methyl iodide in the presence of bases the methylthionitrones (Va, b) are formed exclusively, whereas treatment with diazomethane gives small amounts (~ 5%) of the thiohydroxamic esters (VIIa, b) in addition to compounds (Va, b) (cf. [13]). In this case a more convenient method for the production of compounds (VIIa, b) was the action of the Lawesson reagent on the hydroxamic esters (VIa, b). The aminonitrones (VIII) and (IX) were obtained by the reaction of the methoxynitrones (IV) with ammonia and methylamine [15].



II, IV, VI X=O; III, V, VII X=S; II, IV, VI, VIII a R=CH_3; b R=NO; c R=O⁻;
III, V, VII a R=CH_3; b R=NO; VIII a-c R^1=H; IXa R=R^1=CH_3

In the ^{13}C NMR spectra of the model compounds (IV) and (VI) and compounds (V) and (VII) (Table 1) considerable differences are observed in the chemical shifts of the $C_{(4)}$ carbon atoms contained in the tautomerizing fragments of (II) and (III), i.e., 19 ppm for the methoxy-oxo derivatives (IV, VI) and 54 ppm for the methylthio-thioxo derivatives (V, VII) (Table 2). In addition, appreciable differences are also observed in the positions of the $C_{(2)}$ signals and also, in the case of the S-derivatives, the $C_{(5)}$ signals. The positions of the $C_{(2)}$, $C_{(4)}$, and $C_{(5)}$ signals in the spectra of the OH (II) and SH (III) derivatives are close to the chemical shifts of the corresponding carbon atoms in the spectra of the hydroxamic (VI) and thiohydroxamic (VII) esters, while the differences in the chemical shifts both for the 1-methyl (a) and for the 1-nitroso (b) derivatives are approximately identical and amount to approximately 5% of the total value of the interval (Tables 1 and 2). According to these data, the position of the equilibrium both for the OH and for the SH derivatives (II, III) is shifted significantly toward the oxo (II") and thioxo (III") forms (~ 95%) like the pyridine derivatives [4, 5] and does not depend to an appreciable degree on the effect of the substituent at position 1 of the heterocycle (CH_3 or NO).

The derivatives (II) proved insensitive to change in the solvent (Table 1). In the case of the thio derivatives (III) an increase in the differences between the chemical shifts in the spectra of compounds (III) and (VII) is observed in the transition to carbon tetrachloride (Table 2). This may be due to shift of the equilibrium toward the mercaptonitrone (III') (~15-20%).

In the IR spectra the aminonitrones (VIII) give characteristic bands for the stretching and deformation vibrations of the NH_2 group and the nitrone group, close to the corresponding characteristics in the IR spectra of 2-aminopyrroline N-oxides [3]. The data from the ^{13}C NMR spectra of the amino derivatives (VIII) and (IX) agree with the conclusion in [3] that such compounds exist in the aminonitrone form; the chemical shift of the $C_{(4)}$ atom lies in the region of 140-150 ppm (Table 1), characteristic of nitrones [8, 16].

TABLE 2. The Differences in the Chemical Shifts in the ^{13}C NMR Spectra of the Model Compounds and Tautomeric Systems in Various Solvents

Δδ	$C_{(4)}$	$C_{(2)}$	$C_{(5)}$	Solvent
Hydroxy-oxo derivatives				
δ (VIa) − δ (IVa)	19,2	−8,8	−1,6	DMSO
	16,2	−9,3	−1,5	CCl_4
	14,4	−8,7	−1,7	CH_3OH
δ (VIb) − δ (IVb)	19,0	−7,4; −7,2	−1,3; −1,5	DMSO
δ (IIa) − δ (VIa)	−1,1	−0,3	0,2	DMSO
	1,2	0,8	0,3	CCl_4
	−0,4	0,5	0,9	CH_3OH
δ (IIb) − δ (VIb)	−0,9	−0,2; −0,4	−0,3; −0,2	DMSO
Mercapto-thioxo derivatives				
δ (VIIa) − δ (Va)	54,4	−5,6	4,2	DMSO
	56,1	−6,3	4,5	CCl_4
	48,5	−6,1	3,4	CH_3OH
δ (VIIb) − δ (Vb)	53,7; 52,3	−4,4; −4,7	4,1; 4,0	DMSO
	49,7	−5,3	3,4	CH_3OH
δ (IIIa) − δ (VIIa)	−2,7	−1,2	−1,1	DMSO
	−10,8	−0,3	−0,7	CCl_4
	−5,3	−0,2	−0,7	CH_3OH
δ (IIIb) − δ (VIIb)	−2,9; −2,4	−0,6; −0,1	0; 0,1	DMSO
	−4,3	−0,2	−0,2	CH_3OH

TABLE 3. The Characteristics of the Synthesized Compounds

Compound	Molecular formula	mp, °C*	UV spectrum, λ_{max}, nm (log ε)	Yield, %
IIIa	$C_8H_{16}N_2OS$	100...103	220 (4,05), 265 (3,80), 280 (3,78)	85
IIIb	$C_7H_{13}N_3O_2S$	143...147	235 (3,93), 270 (4,29)	85
Va	$C_9H_{18}N_2OS$	54...58	276 (3,87)	85**
Vb	$C_8H_{15}N_3O_2S$	36...38	233 (4,06), 281 (3,90)	90**
VIa	$C_9H_{18}N_2O_2$	Oil	296 sh (1,95)	80**
VIb	$C_8H_{15}N_3O_3$	47...50	235 (3,78)	85**
VIIb	$C_9H_{18}N_2OS$	Oil	266 (4,02)	70
VII b	$C_8H_{15}N_3O_2S$	44...46	270 (4,29)	40

*Compounds (IIIa, IIIb, VIIa) were recrystallized from ethanol, and (Va, Vb, VIb, VIIb) from hexane.
**The yield during alkylation by method A.

Analysis of the NMR spectra of the nitroxyl radicals (IIc) and (VIIIc) does not make it possible to reach conclusions about the position of the tautomeric equilibrium, since the chemical shifts of the broad signals of the $C_{(4)}$ atom, like the other atoms, are determined mainly by hyperfine coupling with the unpaired electron [17]. However, the close similarity in the IR and UV spectra of compounds (IIc) and (VIIIc) and the spectra of compounds (IIa) and (VIIIa) indicates that the position of the tautomeric equilibrium in them is evidently the same as in the diamagnetic analogs.

In conclusion we note that the chemical shifts of the nitrone atom and the $C_{(4)}$ carbon of the compounds containing the heteroatoms N, O, and S at the α-carbon atom of the nitrone group lie in the same range as the chemical shifts of the protons with C-substituents (137-150 ppm) [16]. The substituent at the $N_{(1)}$ nitrogen atom has an effect of the same type [8], and there is a downfield shift of 4-6 ppm during the formation of a hydrogen bond with the N-oxide oxygen atom [18].

EXPERIMENTAL

The IR spectra were recorded in tablets with potassium bromide and in carbon tetrachloride and chloroform on a UR-20 spectrophotometer. The UV spectra were obtained in ethanol on a Specord UV-Vis spectrophotometer. For the ^{13}C NMR spectra we used the same conditions as in the previous papers of the present series [1, 8, 16, 18]. The elemental analysis was conducted on a Finnigan MAT-8200 mass spectrometer with a resolution of 10,000.

The characteristics of the synthesized compounds are given in Table 3. The data from elemental analysis of compounds (III, V-VII) for C, H, N, and S agree with the calculated data.

3-Hydroxy-1,2,2,5,5,-Pentamethylimidazolidine-4-thione (IIIa). To a solution of 2.0 g of 4-cyano-1,2,2,5,5-pentamethyl-3-imidazoline 3-oxide (Ia) in 50 ml of ethanol we added a solution of 5.6 g of $Na_2S \cdot 9H_2O$ in 10 ml of water. The mixture was left at room temperature for 2 days. The alcohol was then removed at reduced pressure, 20 ml of water was added, the solution was extracted with chloroform, and the extract was dried over magnesium sulfate. After removing the chloroform we obtained 0.34 g of 4-thiocarbamoyl-1,2,2,5,5-pentamethyl-3-imidazoline 3-oxide [11]. To the aqueous solution was added a 7% solution of hydrochloric acid to pH 2. The solution was extracted with chloroform, and the extract was dried over magnesium sulfate. After removal of the chloroform 1.8 g of (IIIa) was obtained.

1-Nitroso-3-hydroxy-2,2,5,5-tetramethylimidazolidine-4-thione (IIIb) was obtained similarly from 1-nitroso-2,2,5,5-tetramethly-1-cyano-3-imidazoline 3-oxide (Ib).

The alkylation of (IIa, b) and (IIIa, b) with methyl iodide (method A) and diazomethane (method B) was conducted according to [19]. The products were separated by column chromatography on silica gel (with chloroform as eluant).

3-Methoxy-1,2,2,5,5-pentamethylimidazolidine-4-thione (VIIa). To a solution of 0.35 g of 3-methoxy-1,2,2,5,5-pentamethylimidazolin-4-one (VIa) in 5 ml of toluene we added 0.6 g of 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (Lawesson's reagent), and we heated the mixture at 100°C for 1 h. After cooling and distillation of the toluene the mixture was separated on a column of silica gel with chloroform as eluant.

3-Methoxy-1-nitroso-2,2,5,5-tetramethylimidazolidin-4-thione (VIIb) was obtained from 3-methoxy-1-nitroso-2,2,5,5-tetramethylimidazolin-4-one (VIb) under analogous conditions.

4-Amino-1,2,2,5,5-pentamethyl-3-imidazoline 3-oxide (VIIIa) ($C_8H_{17}N_3O$). We dissolved 0.5 g of 4-methoxy-1,2,2,5,5-pentamethyl-3-imidazoline 3 oxide (IVa) in 10 ml of a saturated alcohol solution of ammonia and left the solution for 20 h. After distilling the alcohol we washed the residue with a 5:1 mixture of hexane and diethyl ether and filtered off the solid residue. The yield was 0.4 g. M^+ found 171.1369, calculated 171.1372. IR spectrum, ν, 1730 s, 1700 vs, 1640 m cm^{-1}. UV spectrum λ_{max} (log ε): 230 nm (3.98).

4-Amino-1-nitroso-2,2,5,5-tetramethyl-3-imidazoline 3-oxide (VIIIb) ($C_7H_{14}N_4O_2$) and 4-amino-2,2,5,5-tetramethyl-3-imidazoline 3,1-dioxide (VIIIc) ($C_7H_{14}N_3O_2$) were obtained from (IVb) and (IVc) under analogous conditions [19]. Compound (VIIIb), M^+ found 186.1120, calculated 186.1117. IR spectrum, ν: 1690 vs, 1620 s cm^{-1}. UV spectrum, λ_{max} (log ε): 235 nm,. Compound (VIIIc), M^+ found 172.1103,m calculated 172.1086. IR spectrum, ν: 1690 vs, 1620 s cm^{-1}. UV spectrum λ_{max} (log ε): 236 nm (4.00).

4-Methylamino-1,2,2,5,5-pentamethyl-3-imidazoline 3-oxide (IXa) ($C_9H_{19}N_3O$) was obtained similarly from (IVa) with a saturated alcohol solution of methylamine. M^+ found 185.1528, calculated 185.1528. IR spectrum, ν: 1710 vs, 1690 m cm^{-1}. UV spectrum, λ_{max} (log ε): 244 nm (3.95).

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SYNTHESIS OF 1-(3,5-DI-tert-BUTYL-4-HYDROXYPHENYL)-2-R-BENZIMIDAZOLES

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UDC 547.785.5+547.563+547.567

Reaction of 2,6-di-tert-butyl-1,4-benzoquinone with o-phenylendiamine gives 2,6-di-tert-butyl-1,4-benzoquinone-4-(N-o-aminophenyl)imine which reacts smoothly with heterocyclic, aromatic and aliphatic aldehydes to form (1-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-substituted benzimidazoles.

It is known that some nitrogen heterocycles, including imidazole and benzimidazole, which contain a 2,6-di-tert-butylphenol residue possess anti-inflammatory and analgesic activity [1] and show anti-oxidant properties [2].

Bisazomethines based on o-phenylendiamine cyclize to form benzimidazole [3]. The reaction conditions decide whether a single compound or a mixture of several substances are formed.

Reaction of 2,6-di-tert-butyl-1,4-benzoquinone with substituted anilines leads to the corresponding iminoquinones [4] but the reaction of this quinone with o-phenylendiamine has not been studied. We have found that reaction of the quinone occurs with one of the amino groups to form the iminoquinone I.

Heterocyclic, aromatic, and aliphatic aldehydes react vigorously with I, apparently via the azomethine iminoquinones II. Further conversion to the benzimidazoles III is possible only through the intramolecular oxidation-reduction of the azomethine bond and the iminoquinone molecular fragment.

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