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<sup>13</sup>C NMR SPECTRA OF CYCLIC NITRONES.

1. 2-SUBSTITUTED 4-METHYL- AND 4-PHENYL-1-HYDROXY-5,5-DIMETHYL-3-IMIDAZOLINE 3-OXIDES

I. A. Grigor'ev, V. V. Martin, G. I. Shchukin,  
V. I. Mamatyuk, and L. B. Volodarskii

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The introduction of an N-oxide oxygen atom into azomethines leads to an upfield shift of the signals for the carbon atom of the C=N group in the <sup>13</sup>C NMR spectra by 30-33 ppm. This is consistent with the increase in the electron density on this atom. The signal of the nitron carbon atom is observed in the region of 140-147 ppm, depending on the nature of the substituent at the C(2) atom of the 3-imidazoline 3-oxide ring.

Cyclic nitrones, which are heterocyclic compounds containing an azomethine N-oxide group, have a wide range of synthetic potentialities [1]. This is due to the fact that, as in the case of heterocyclic N-oxides [2], the N-oxide oxygen atom activates them with respect both to electrophilic and to nucleophilic and radical reagents. In addition, the ability of the nitrones to undergo 1,3- and 1,4-cycloaddition reactions makes it possible to use them in the synthesis of various heterocyclic systems, including natural compounds [3, 4]. There are no published data on the systematic investigation of compounds containing a nitron group by <sup>13</sup>C NMR spectroscopy, whereas this method makes it possible not only to obtain valuable structural information but also to assess the electron density distribution in the ground state of the molecule [5, 6].

In the present work we begin a series of investigations into cyclic nitrones by <sup>13</sup>C NMR spectroscopy on the basis of 3-imidazoline 3-oxides in order to determine the characteristic range of chemical shifts (CS) of the carbon atoms of the nitron group and also to study the effect of various factors (substituents, solvents, etc.) on the electron density distribution in the ground state of a molecule containing the nitron group. In the present work we considered the effect of substituents at the second position of 3-imidazoline 3-oxide.

It is known that the N-oxide group in pyridine N-oxides has a strong electron-donating effect on the α- and γ-carbon atoms [7]. An effect similar in direction but larger in magnitude by virtue of its greater localization is observed in nitrones. Thus, during comparison of the spectra of the 3-imidazolines (Ia) and (IIIa) with the spectra of the corresponding 3-imidazoline 3-oxides (IIa) and (IVa) a strong screening effect on the C(4)

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Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from *Khimiya Geterotsiklicheskikh Soedinenii*, No. 2, pp. 247-251, February, 1985. Original article submitted March 12, 1984.

TABLE 1. The  $^{13}\text{C}$  NMR Spectra of 3-Imidazolines (Ia, IIIa) and 3-Imidazoline 3-Oxides (IIa,b,e,f, IVa-f)

Compound	X	$\text{C}_{(4)}^a$	$\text{C}_{(2)}$	$\text{C}_{(5)}$	4- $\text{CH}_2$ of $\text{C}_4$	ortho	meta	para	2- $\text{CH}_2$ of 5- $\text{CH}_3$	X
Ia	$\text{CH}_3$	173.4 (-31.2)	88.4 (+1.6)	70.3 (-3.9)	15.5 (-6.6)				26.1 & 22.9	
IIa	$\text{CH}_3$	142.2	90.0	66.4	8.9				23.4 & 23.8	
IIb	H	143.8	84.5	67.5	8.7				23.7; 17.6 & 15.6	
IIe	$\text{C}(=\text{NOH})\text{CH}_3$	145.7	94.3	68.2	9.0				26.2; 20.5 & 16.1	154.5; 9.2
IIf	$\text{COCH}_3$	147.2	94.9	70.6	9.0				25.3; 21.0 & 14.1	202.9; 22.7
IIIa	$\text{CH}_3$	172.1 (-32.3)	87.8 (+1.7)	69.9 (-4.0)	133.0 (-5.8)	127.5 (-0.6)	128.4 (-0.7)	130.1 (-1.3)	26.2 & 24.1	
IVa	$\text{CH}_3$	139.8	89.5	65.9	127.2	126.9	127.6	128.8	23.7 & 24.4	
IVb	H	141.0	84.9	68.5	127.8	127.2	128.2	129.9	24.8; 19.7 & 15.0	
IVc	$\text{CHOHCH}_3$	142.2	92.9	67.6	127.8	127.8	128.3	129.7	27.4; 21.6 & 16.3	
IVd	$\text{C}(=\text{NNHCH}_3)\text{CH}_3$	142.0	94.8	67.6	127.8	127.5	128.3	129.6	27.7; 21.4 & 15.8	69.4; 17.3
IVe	$\text{C}(=\text{NOH})\text{CH}_3$	142.6	94.1	68.2	127.5	127.5	128.4	129.9	27.5; 21.6 & 16.1	142.0; 37.5 & 10.1
IVf	$\text{COCH}_3$	143.6	94.4	70.1	126.9	127.6	128.4	130.2	26.7; 22.0 & 14.0	154.4; 9.1 201.3; 22.5

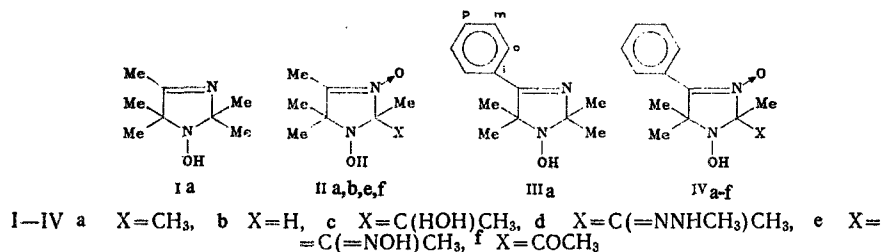
<sup>a</sup>The values of the relative chemical shifts are given in parentheses: for (Ia),  $\delta$ (IIa) -  $\delta$ (Ia); for (IIIa),  $\delta$ (IVa) -  $\delta$ (IIIa).

TABLE 2. The Total ( $Q_{\sigma+\pi}$ ) and  $\pi$  Charges ( $Q_{\pi}$ ), Calculated by the CNDO/2 Method, at the Atoms of the Nitron and Imine Groups in the Model Compounds (V–XIII) and the Calculated Values of the Relative Chemical Shifts  $\Delta\delta^{13}\text{C}^a$

Compound	$Q_{\sigma+\pi} \cdot 10^2$			$\Delta\delta^{13}\text{C}, \text{ppm}$	$Q_{\pi} \cdot 10^2$			$\Delta\delta^{13}\text{C}, \text{ppm}$
	C	N	O		C	N	O	
V	+152	-191			+92	-141		
VI	+30	+237	-440	-27 <sup>b</sup>	-82	+832	-785	-28 <sup>b</sup>
VII	+135	-176			+63	-101		
VIII	+3	+237	-442	-29 <sup>c</sup>	-98	+855	-770	-26 <sup>c</sup>
IX	+50	+235	-433	+4 <sup>d</sup>	-44	+803	-802	+6 <sup>d</sup>
X	+31	+246	-398	0 <sup>d</sup>	-137	+844	-740	-9 <sup>d</sup>
XI	+38	+238	-437	+1 <sup>d</sup>	-85	+838	-789	-0.5 <sup>d</sup>
XII	+2	+245	-435	-6 <sup>d</sup>	-96	+843	-780	-2 <sup>d</sup>
XIII	+34	+246	-427	6 <sup>d</sup>	-106	+834	-781	-4 <sup>d</sup>

Note. a) The relative chemical shift with variation of the charge at the C atom was determined by means of the equation  $\Delta\delta = f \cdot \Delta Q$ , where  $f = 220 \text{ ppm/e}$  for  $Q_{\sigma+\pi}$  and  $f = 160 \text{ ppm/e}$  for  $Q_{\pi}$  [6]. b) The expected difference in the chemical shifts of (VI) and (V),  $\Delta\delta = \delta(\text{VI}) - \delta(\text{V})$ , was calculated from the difference between the charges at the carbon atoms by means of the formulas given above. c) The expected difference in the chemical shifts of (VIII) and (VII):  $\Delta\delta = \delta(\text{VIII}) - \delta(\text{VII})$ . d) The expected difference in the chemical shifts at the carbon atoms in compounds IX–XIII compared with (VI):  $\Delta\delta = \delta(\text{IX–XIII}) - \delta(\text{VI})$ .

atom of the nitron group is observed for the latter (Table 1).



The upfield shift of the signal for the C(4) atom in both cases has a similar value (about -32 ppm), approximately equal to the analogous overall effect in pyridine N-oxides at the C(2), C(4), and C(6) atoms ( $\Delta\delta_{\text{C}(2)} + \Delta\delta_{\text{C}(4)} + \Delta\delta_{\text{C}(6)} \approx -33 \text{ ppm}$ ) [7]. Such an upfield shift with the introduction of the N-oxide group is clearly due to the increase in the electron density at the carbon atom of the nitron group compared with the carbon atom of the imine group. In the general case the relation between the chemical shift and the electron density for the carbon atoms is complex, but within the limits of related groups of compounds it is widely used to form an opinion about electronic structures. Table 2 gives the results from a quantum-chemical calculation of the total ( $Q_{\sigma+\pi}$ ) and  $\pi$  charges ( $Q_{\pi}$ ) by the CNDO/2 method for the simple model compounds  $\alpha$ -methylimine (V),  $\alpha$ -methylnitrone (VI),  $\alpha$ -phenylimine (VII), and  $\alpha$ -phenylnitrone (VIII). They closely reflect the tendency and magnitude of the variation in the  $^{13}\text{C}$  chemical shift with variation in the charge at the nitron carbon atom.

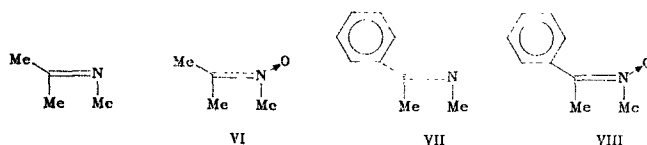


TABLE 3. The Effect of Substituents X on the Relative Chemical Shifts<sup>a</sup> in the Spectra of Compounds (IIa, b, e, f, IVa-f)

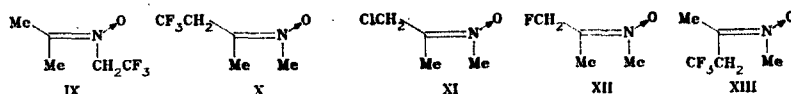
Compound	X	$\Delta\delta_{C(4)}$	$\Delta\delta_{C(2)}$	$\Delta\delta_{C(5)}$	$\Delta\delta_{4-CH_3}$ or $C_i$
IIa	CH <sub>3</sub>	-1,6	+5,5	-1,1	+0,2
IIe	C(=NOH)CH <sub>3</sub>	+1,9	+9,8	+0,7	+0,3
IIf	COCH <sub>3</sub>	+3,4	+10,4	+3,1	+0,3
IVa	CH <sub>3</sub>	-1,2	+4,6	-2,6	-0,6
IVc	CHOHCH <sub>3</sub>	+1,2	+8,0	-0,9	0
IVd	C(=NNHCH <sub>3</sub> )CH <sub>3</sub>	+1,0	+9,9	-0,9	0
IVe	C(=NOH)CH <sub>3</sub>	+1,6	+9,2	-0,3	-0,3
IVf	COCH <sub>3</sub>	+2,6	+9,5	+1,6	-0,9

Note. a) Positive differences in the chemical shifts  $\Delta\delta = \delta(\text{IIa, e, f}) - \delta(\text{IIb})$  and  $\Delta\delta = \delta(\text{IVa, c-f}) - \delta(\text{IVb})$  correspond to a downfield shift.

A screening effect from the N-oxide oxygen atom is also observed for both carbon atoms added to the nitron carbon atom, i.e., 4-CH<sub>3</sub> (IIa) or C<sub>4</sub> (IVa) and C<sub>(5)</sub> (IIa, IVa), and also for all the carbon atoms of the phenyl ring in (IVa) (Table 1). On the other hand, the increase in the electron-withdrawing character of the N<sub>(3)</sub> atom with the introduction of the N-oxide oxygen atom leads to a downfield shift of the signal for the C<sub>(2)</sub> atom.

Thus, the introduction of the N-oxide atom has a strong electron-donating effect on the carbon atom of the C=N group, a weaker electron-donating effect on the carbon atoms attached to it and the  $\alpha$ -phenyl group, and a small electron-withdrawing effect on the C<sub>(2)</sub> atom attached to the nitrogen atom.

Although the introduction of the N-oxide group into the azomethine fragment plays a determining role in the electron density distribution in the nitron group and in the heterocycle of 3-imidazoline 3-oxide as a whole, the introduction of substituents at one or the other position of the ring can lead to some redistribution of electron density, and this in turn must show up in a change of the chemical shifts in the NMR spectra. For the purpose of possibly predicting the direction and scale of the change in the chemical shifts under the influence of the substituents we undertook calculations of the total ( $Q_{O+\pi}$ ) and  $\pi$  charges ( $Q_{\pi}$ ) in the simple model compounds (IX-XIII), which contain substituents with strong electron-withdrawing character at various positions in relation to the nitro group (a -I effect).



Analysis of the data presented in Table 2 makes it possible to reach the following conclusions. The appearance of the electron-withdrawing substituent at the carbon atom attached to the nitrogen atom of the nitron model [model (IX)] must lead to descreening of the nitron carbon atom, i.e., to a downfield shift of the C=N signal. However, as in ketones [5], increase in the electron-withdrawing character of the substituent at the  $\alpha$ -carbon atom [models (X-XIII)] will lead to the opposite effect, i.e., to an upfield shift of the signal for the nitron carbon atom in the <sup>13</sup>C NMR spectrum. The effect of substituents at the  $\alpha$  position on the shift of the signals for the nitron carbon atom will be examined in greater detail in the next communication.

The effects of the substituents X for the methylnitrones (IIa, e, f) and phenylnitrones (IVa, c-f) calculated from the <sup>13</sup>C NMR spectra (Table 1) in comparison with the corresponding "unsubstituted" compounds (IIb) and (IVb) are given in Table 3. Since the skeleton of the compounds does not change, it could be expected that the observed changes in the <sup>13</sup>C NMR spectra were mainly due to the electronic effect of the substituent X. According to the data in Table 3, variation of the substituent X has an appreciable effect on the change in the chemical shifts of the carbon atoms of the nitron groups, and with increase in its electron-withdrawing character (from top to bottom in the table) the signals of the C<sub>(4)</sub> atoms are shifted downfield in accordance with the decrease in the electron density on them [Table 2, model (IX)]. The range of variation of the chemical shifts for the C<sub>(4)</sub> atoms in the <sup>13</sup>C NMR

spectra of the methyl nitrones (II) amounts to about 5 ppm [from (IIa) to (IIf)], while in the phenyl nitrones (IV) it amounts to about 4 ppm [from (IVa) to (IVf)]. The signals for the C(2) and C(5) atoms undergo an analogous downfield shift.

Thus, analysis of the chemical shifts of the carbon atoms in the  $^{13}\text{C}$  NMR spectra makes it possible to form an opinion about the electron density distribution in the ground state of 3-imidazoline 3-oxide molecules.

#### EXPERIMENTAL

The  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Physik AG HX-90 spectrometer at 22.63 MHz by a pulsed technique. For the measurements we used 10-15% solutions of the compounds in DMSO, and to stabilize the resonance conditions at the deuterium nuclei we added ~10% of DMSO- $d_6$ . The chemical shifts were measured with reference to the signal of the solvent (40.4 ppm from TMS,  $\delta$  scale), and the accuracy of the measurements was  $\pm 0.05$  ppm. The signals were assigned on the basis of a comparison of the intensities in the spectra with complete suppression of the spin-spin coupling of the  $^{13}\text{C}$  and  $^1\text{H}$  nuclei and also with allowance for the multiplicity and residual splitting in the spectra with off-resonance decoupling. The quantum-chemical calculations were made by CNDO/2 method using the VIKING set of programs (the NMR laboratory, Moscow State University) on a BESM-6 computer. The geometric parameters of the nitron group in the model compounds (VI, VIII-XIII) and of the imine group in compounds (V, VII) were taken from the data from x-ray crystallographic analysis for 3-imidazoline 3-oxides [8]. The parameters of the substituents were taken from [9].

The synthesis of compounds (Ia, IIIa) [10], (IIa, IVa) [11], (IIb, IVb) [12], (IIe, f) and (IVe, f) [13], and (IVd) [14] have been described before.

1-Hydroxy-2-(1-hydroxyethyl)-2,5,5-trimethyl-4-phenyl-3-imidazoline 3-Oxide (IVc). To a solution of 1 g (3.8 mmoles) of (IVf) in 10 ml of ethanol we added a solution of 0.2 g (5.3 mmoles) of sodium borohydride in 5 ml of water. The mixture was left for 1 h. The ethanol was evaporated, 10 ml of water was added to the residue, the mixture was extracted with chloroform, and the extract was dried and evaporated. The residue was chromatographed on a column of silica gel with ether as eluant. The two diastereomeric compounds (IVc) were isolated successively with yields of 28% (mp 196-198°C, from ethanol. Found %: C 63.3; H 7.6; N 10.8.  $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3$ . Calculated: C 63.6; H 7.6; N 10.6%) and 58% (mp 107-109°C, from ethanol. Found %: C 63.4; H 7.5; N 10.3%). The  $^{13}\text{C}$  NMR spectrum is given.

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